Quantifying Frequency Modulation in Seizures of Patients Undergoing Responsive Neurostimulation

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Rationale. A qualitative analysis of the seizures of patients undergoing Responsive Neurostimulation (RNS) treatment recently showed that responders were more likely to have signs of "indirect frequency modulation" than non-responders (Kokkinos et al., JAMA Neurol. 2019). Such modulation was characterized by a shift in power across spectral bands over several months of RNS treatment. To assess the significance of this finding quantitatively, we develop a method for measuring the extent of indirect frequency modulation in intracranial electrophysiological data of patients chronically implanted with RNS systems. Using a seizure segmentation tool we developed earlier (Venkatesh et al., AES 2019), we quantify indirect frequency modulation between RNS programming epochs using an Earthmover's distance on the distribution of seizure segments in normalized frequency-power space.

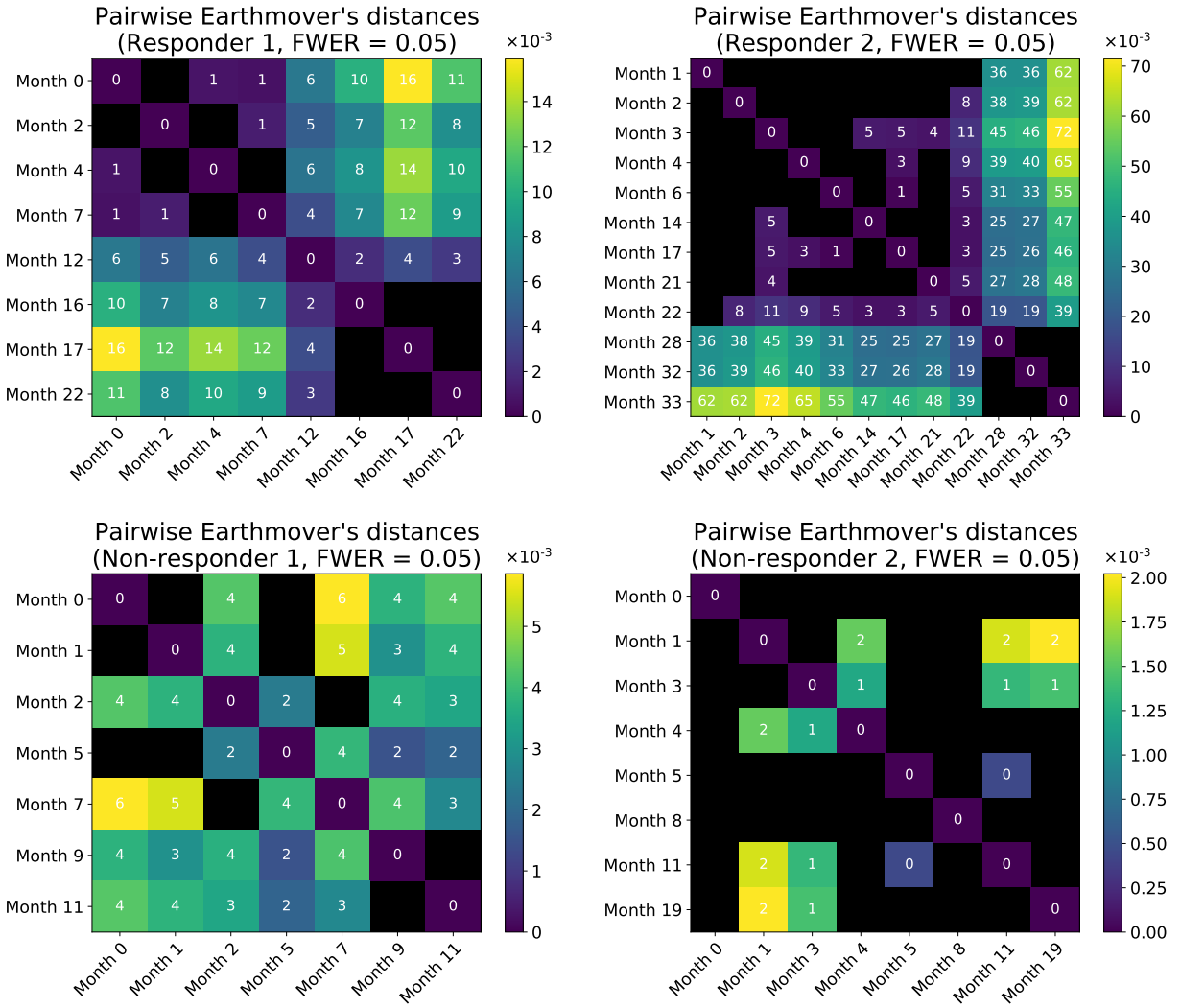
Methods. Seizure data of 13 patients implanted with RNS systems (NeuroPace Inc.), five of whom showed indirect frequency modulation in a qualitative analysis, were considered. Each patient's data consisted of several "programming epochs", corresponding to a different set of RNS stimulation parameters. We quantified frequency modulation as follows: (1) Starting with electrographic data marked for seizure onset, we used an automated seizure segmentation algorithm to partition each seizure into segments containing distinct frequency signatures (Venkatesh et al., AES 2019). (2) We then represented each seizure segment as a 3-dimensional vector using the average energy in three frequency bands (0-10Hz, 10-30Hz and 30-60Hz). Each vector was then L1-normalized to discount effects of unknown electrode impedance across patients. (3) To evaluate indirect (long-term) frequency modulation, we pooled segments from all seizures of each programming epoch and computed the empirical distribution of the segments in each epoch (weighting each segment according to its duration). (4) We then measured frequency modulation between two epochs using the Earthmover's distance between the empirical distributions of their segments. Intuitively speaking, the Earthmover's distance measures the minimum "work" required to move the mass of one distribution so as to make it equal to the other. (5) Finally, for every pair of epochs, we estimated the significance of the Earthmover's distance against a null hypothesis of zero distance by using a permutation test, and reported all distances that were significant at a family-wise error rate of 5% for each patient.

Results. The figures show pairwise Earthmover's distances across all programming epochs (labelled by month from baseline) for each patient; e.g., the first row represents the distance from the first valid epoch to each subsequent epoch. Patients who responded (with indirect frequency modulation in the qualitative analysis) showed a sustained increase in Earthmover's distance after a

certain programming epoch relative to non-responders. Some responders also showed increases of larger magnitudes relative to non-responders.

Conclusions. We developed a metric to quantify indirect frequency modulation in patients undergoing RNS. Our Earthmover's distance-based measure matches a qualitative assessment, and shows promise as a predictive metric for tuning RNS stimulation parameters, evaluating RNS efficacy, and predicting long-term clinical outcomes.

Indirect Frequency Modulation in Exemplar Responders and Non-responders



Each plot shows a quantification of indirect frequency modulation for a particular patient: each cell in the matrix represents the Earthmover's distance between two programming epochs (only cells that were significant at a family-wise error rate of 5% are depicted; the rest are shown in black). The plots show that responders have a sustained change in the frequency content of their seizures: this is evidenced by large values in two distinct off-diagonal blocks while diagonal blocks are close to zero, or insignificant. In contrast, non-responders show no clear structure, and distances are often small or statistically insignificant.