Individualized seizure cluster prediction using machine learning and ambulatory intracranial EEG

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***Abstract*—Seizure clusters, i.e., seizures that occur within a short duration of each other, occur in several epilepsy patients and are associated with increased disease severity. Understanding the characteristics of seizure clusters and predicting whether a given seizure will cluster or not is valuable both from a patient's and clinician's perspective. We propose a novel methodology for studying seizure clusters based on bivariate intracranial EEG (iEEG) features and develop one of the first individualized seizure cluster prediction models by combining machine learning with relative entropy (a bivariate feature). Relative entropy was used to quantify interactions between brain regions and capture potential differences in interactions underlying isolated and cluster seizures. We evaluated our methodology using one of the largest ambulatory iEEG datasets, consisting of data from 15 patients with up to 2 years of recordings each. This provided us a sufficient n umber o f s eizures i n e ach p atient to enable individualized analyses and prediction. On data of 3710 seizures consisting of 3341 cluster seizures (from 427 clusters) and 369 isolated seizures, machine learning models based on relative entropy predicted seizure clusters with up to 73.6% F1-score and outperformed baseline predictors. Our results are beneficial in addressing the clinical burden of clusters.**

***Index Terms*—seizure clusters, relative entropy, intracranial EEG, seizure cluster prediction, bivariate feature**

I. Introduction

Seizures in an individual can follow a range of patterns from cyclic, to random, to clustered [1], [2]. Seizure clustering, i.e., the occurrence of multiple seizures within a short duration, is estimated to occur in 13% - 76% of epilepsy patients [3]. A long-term Finnish prospective observational study found that people with seizure clusters had worse disease outcomes than those without clusters [4]. Patients more likely to experience seizure clusters are given stronger anticonvulsant medications, which may cause side effects [5]. These drugs are administered preemptively since, on termination of a given seizure, it is unknown whether another seizure will occur in the near future. Predicting whether another seizure will occur shortly after the termination of a seizure, i.e., whether a seizure will cluster, is clinically important. Our goal is to develop individualized machine learning (ML) models for predicting seizure type, i.e., isolated seizure or cluster seizure, using intracranial EEG (iEEG) data. iEEG may capture differences in seizure dynamics, i.e., brain activity of different seizure types in patients with drug-resistant epilepsy [3], [5].

The main challenges in predicting seizure types are: (i) the lack of long-term EEG data of individuals, (ii) limited understanding of the differences between isolated and cluster seizures, and (iii) limited exploration of ML methods that are suitable for individualized cluster prediction. Ferastraoaru et al. observed differences in the duration of isolated and cluster seizures by pooling short-term data from 92 patients but had limited samples from each patient ($3 - 31$ seizures each) to explore patient-specific differences [6]. However, the patient-specific nature of seizure dynamics suggests that differences between isolated and cluster seizures might be patient-specific [2]. Karoly et al. found differences in the pre-ictal iEEG energy between isolated and cluster seizures in three out of 15 patients in long-term NeuroVista data [7]. However, they did not explore more fine-grained iEEG features, for e.g., bivariate features, which may further highlight patient-specific differences. To the best of our knowledge, previous studies have not developed individualized seizure cluster prediction

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methods.

We propose a novel approach for predicting individualized seizure type using ML and a bivariate feature extracted from various physiologic frequency bands from long-term iEEG data. (i) We used various frequency bands because the band capturing prominent seizure-related iEEG changes can vary across patients [8]. (ii) We used relative entropy (REN), a bivariate feature, because it can quantify the dynamics underlying different seizure types. Epilepsy is increasingly being understood as a network disorder [9], [10]. We expect that if the dynamics of isolated and cluster seizures are different, their network interactions, measured using the similarity in iEEG between pairs of electrodes, might show differences [11]. (iii) We used individualized long-term iEEG data to capture a sufficient number of seizures in each patient to enable exploration of patient-specific differences in dynamics [2] and training of individualized models. (iv) Finally, we trained several linear and non-linear ML models using REN data as features to predict seizure type.

We evaluated our approach using NeuroVista data [12], one of the largest ambulatory iEEG datasets, consisting of data from 15 patients with up to 2 years of recordings for each patient. The analysis included 3710 isolated and cluster seizures. Seizures within 24 hours of each other were considered as belonging to a cluster. For each seizure, iEEG data from the ictal as well as 10 minutes pre-ictal period (*near-seizure*) were used. We computed REN from the iEEG data since it has previously been used for seizure detection [13] and seizure onset zone localization [11]. To evaluate whether REN captures differences in seizure types, averaged REN values in different frequency bands for isolated and cluster seizures were statistically compared [2]. Based on insights from the statistical analysis, we developed several individualized prediction models and compared them with baseline techniques for predicting seizure cluster. Finally, we assessed the robustness of our results by repeating the analyses with seizures within 8 hours of each other being considered as part of a cluster.

Our contributions are as follows:

1) We proposed a generic framework (Fig. 1, Fig. 2) for investigating the dynamics of cluster seizures and for predicting if a given patient will experience a seizure cluster or an isolated seizure.
2) Using REN from various frequency bands, we found significant differences between the dynamics of isolated and cluster seizures in six patients, substantially improving over a previous approach that found differences only in three patients on the same dataset.
3) We found that the majority of the differences were in the beta and gamma bands and during the near-seizure period.
4) Individualized ML models predicted seizure type with 73.6% F1-score and outperformed baseline predictors. To the best of our knowledge, this is the first demonstration of individualized seizure cluster prediction.
5) The results were robust to change in the inter-seizure interval threshold for clustering.

The prediction models can be clinically useful in guiding the selection of anticonvulsant medications based on seizure type. Moreover, insights into the characteristics of seizure clusters can guide the exploration of techniques to mitigate their clinical burden, for e.g., through changes in brain stimulation parameters.

II. Methods

The overall analyses pipeline is shown in Fig. 1. The details of each step are described below.

A. Long-term iEEG data collection

We used data that was collected as part of the NeuroVista study in Australia [12]. In that study, 15 patients with refractory epilepsy were implanted with an intracranial EEG device that collected data in an ambulatory setting for up to 2 years in each patient. Data from six patients was excluded from this study due to significant data drops which could affect the analysis of clustering. The nine patients included in the study had an average recording duration of 550 ± 208 days. Data for each patient consisted of iEEG data collected from 16 electrodes (2 lead assemblies with 8 contacts distributed across 2 electrode arrays each) placed on the presurgically assessed seizure onset zone. Data was sampled at 400Hz and wirelessly transmitted from the implanted device to an external, handheld personal device.

B. Seizure detection and the selection of near-seizure data

Seizures were detected from the iEEG data for each patient using a published methodology [14]. This procedure resulted in an average of 412.2 ± 348.4 seizures per patient over the course of their entire recording. The average duration of the seizures was 39.0 ± 63.6s. Since pre-ictal activity near seizure onset can show differences between different seizure types [7], we included pre-ictal iEEG in our analysis. For each seizure, pre-ictal iEEG up to 10mins prior to seizure onset was considered because seizure-related changes can manifest in that duration [15]. In case a seizure had occurred within the previous 10 mins of the given seizure, the iEEG data between the termination of the previous seizure and the onset of the given seizure was considered. We refer to this pre-ictal iEEG data as *near-seizure*.

C. iEEG preprocessing

iEEG data was preprocessed as follows. First, since ambulatory recordings can have several artifacts, we used a bipolar montage for referencing the signals. Bipolar montage was computed by taking the difference between the iEEG signals on consecutive channels on each array, resulting in 12 bipolar pairs (2 lead assemblies $\times$ 2 arrays $\times$ 3 bipolar pairs per array) per patient. For clarity, we refer to each bipolar pair as an "electrode" for the remainder of the analysis unless otherwise stated. Seizure and near-seizure iEEG data from each electrode was divided into 2.5s non-overlapping

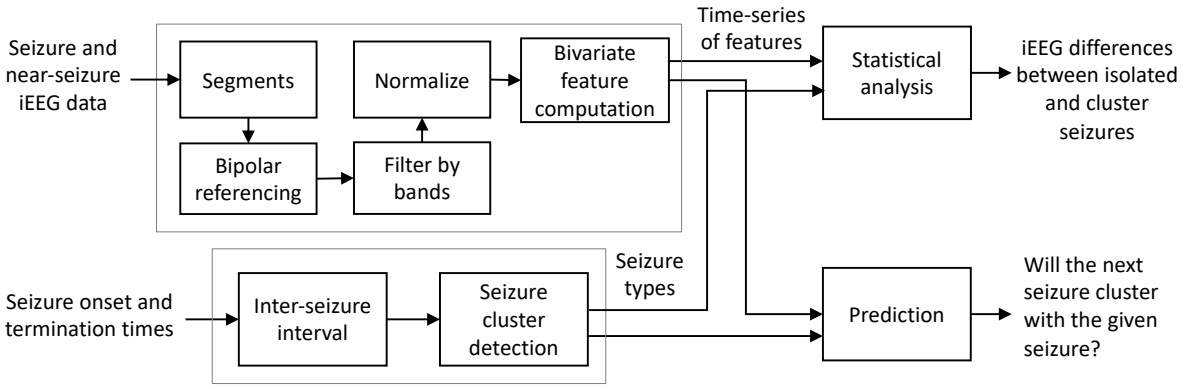

Fig. 1. Analysis pipeline.

segments. Segment length was chosen as 2.5s to provide a sufficient number of samples in each segment to robustly estimate relative entropy. Segments in seizure and near-seizure periods were aligned to seizure onset. Additional artifact removal was not done because the iEEG data used for the analysis was of a short duration and since bipolar montage can remove artifacts that are common across channels. Data in each segment was filtered into the following physiologic bands for feature extraction: delta (0.5 – 4Hz), theta (4 – 8Hz), alpha (8 – 12Hz), beta (12 – 25Hz), and gamma (25 – 45Hz) using 2^{nd} order Butterworth bandpass filters. The resulting timeseries for each band and electrode within a segment was independently normalized to have zero mean and unit variance.

D. Seizure cluster detection

Seizure clusters were identified based on the inter-seizure intervals (ISIs) of successive seizures. Several definitions for seizure clusters have been proposed in literature based on a cutoff for the ISI, ranging from 2 hours to 24 hours [6], [16]. For this analysis, we used 24 hours as the cutoff since it is widely used. Based on this definition, seizures were categorized into the following three types: (i) *Isolated* seizures were seizures that did not have a seizure 24 hours before or after them. The remaining seizures were categorized as cluster seizures. Cluster seizures were further categorized into (ii) *cluster-last*, which were the last seizures in clusters, and (iii) *cluster-non last*, which were seizures in a cluster that were not the last seizure. Seizures within clusters were subcategorized to study differences and similarities between those subcategories and isolated seizures. Near-seizure iEEG segments were considered to be in the same category as their corresponding seizure. To assess the robustness of our results to the definition of seizure clusters, we also evaluated all the results for an 8 hour cutoff for the ISI.

E. Bivariate feature computation

We used relative entropy (REN), a bivariate feature, for analysing the iEEG data. REN quantifies the dissimilarity in the distribution of iEEG signal amplitudes between two electrodes. REN was computed for each segment and band separately. For a given pair of electrodes, the distributions of amplitudes of the filtered signals were compared using KL divergence. Since KL divergence is nonsymmetric, the dissimilarity was measured with each signal as reference and the maximum was considered as REN [11]. REN was computed for all pairs of electrodes within a patient.

F. Statistical analyses

We statistically compared REN values for the different types of seizures separately for each band. Since we were primarily interested in differences between isolated and cluster seizures, in each scenario two comparisons were done: (i) isolated vs cluster-last and (ii) isolated vs cluster-non last. Wilcoxon rank sum test was used for statistical comparison, and FDR correction was applied to correct for multiple testing in each analysis.

G. Machine learning prediction models

We tested several linear and non-linear classification methods for predicting seizure clustering (Fig. 2). The linear models evaluated in this study were logistic regression and support vector machine (SVM). Among non-linear classifiers, random forest, decision trees, and k-nearest neighbors (k-NN) were evaluated. For each classifier, we used 5-fold cross validation with 80%-20% training-testing split of the patient's data. Classifiers were individualized by only training and testing on data of the same patient. Since each method had several hyper-parameters that could affect model performance, we used inner 5-fold cross validation for selecting hyper-parameters using only the training data (which was split into training and validation sets). Hyper-parameters for each classifier were as follows: logistic regression (solver: ["newton-cg", "lbfgs", "liblinear"], penalty= "l2", C: [100, 10, 1.0, 0.1, 0.01]), SVM (kernel: ["poly", "rbf", "sigmoid"], C: [50, 10, 1.0, 0.1, 0.01], gamma: [1, 0.1, 0.01, 0.001, 0.0001]), random forest (bootstrap=True, max_depth: [2, 3], min_samples_leaf: [4, 5]), decision tree (max_depth: [2, 3], min_samples_leaf: [4, 5], criterion: ["gini", "entropy"]). Due to imbalance in class sizes, samples were weighted inversely proportional to class size during model training. We used precision, recall, F1-score, and

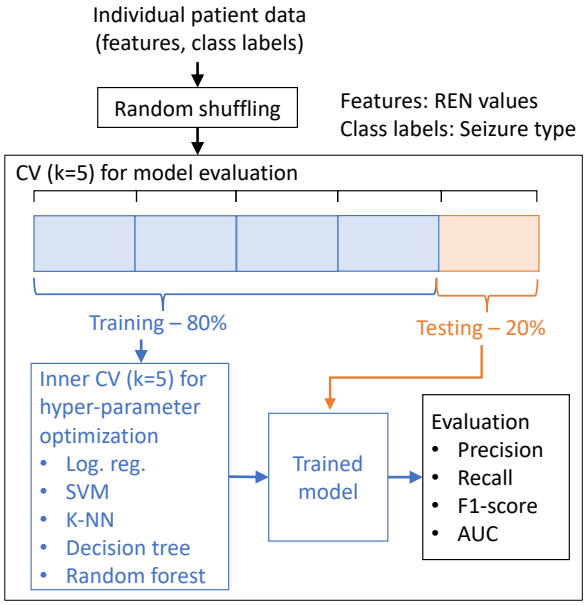

Fig. 2. Workflow for developing and evaluating seizure cluster prediction models. Abbreviations: CV, cross-validation; log. reg., logistic regression.

area under the receiver operation characteristics curve (AUC) as performance metrics.

Each prediction model used REN values from the different bands and periods as input and predicted whether the next seizure would occur within 24 hours of the given seizure or not. For this task, seizures were divided as follows: (i) "isolated + cluster-last" - isolated seizures and the last seizure in clusters, since no seizure occurs shortly after them; and (ii) "cluster-non last" - the remaining seizures in clusters. During robustness analysis, the same classes were used although the model predicted whether the next seizure would occur within 8 hours of the given seizure or not.

We compared the models with two baseline predictors: (i) a chance-level predictor (*baseline 1*), and (ii) a model that always predicts "cluster", i.e., another seizure will occur soon (*baseline 2*). The theoretical performance for the baseline predictors were calculated as follows. Assume that the true probability of a seizure to be cluster-non last is r, and the model predicts the cluster-non last label with probability q. Then, the precision is r for both *baseline 1* and *baseline 2*. The recall is q for *baseline 1* and 1 for *baseline 2*. Thus, the F1 score for *baseline 1* is $\frac{2rq}{r+q}$, and the F1 score for *baseline 2* is $\frac{2r}{r+1}$. The AUC for *baseline 1* is 0.5 and the AUC for *baseline 2* can not be computed.

III. Results

A. Distribution of seizure type per patient

We observed seizures of both types in all the patients (Fig. 3). The ratio of isolated to cluster seizures varied across patients. For example, patients 3, 4, and 6 have very few isolated seizures compared to cluster seizures, whereas, patient

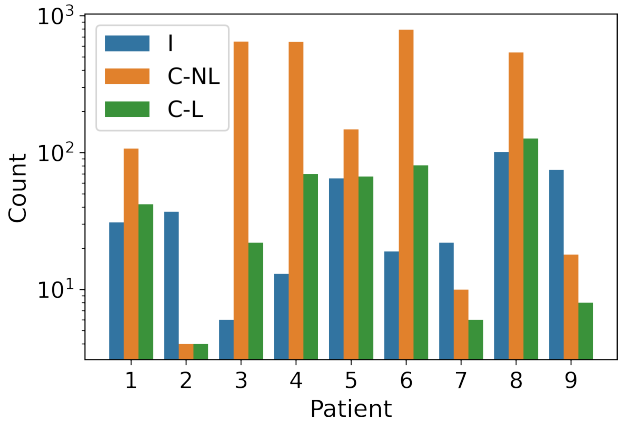

Fig. 3. Data summary. Number of seizures of each type in each patient. Y-axis is shown in log scale. Abbreviations: I, isolated seizure; C-L, cluster-last seizure; C-NL, cluster-non last seizure.

9 had many more isolated seizures than cluster seizures. The ratio of isolated to cluster seizures varied from 0.01 - 4.63. Across all patients, there were a total of 369 isolated seizures, 2914 cluster-non last seizures, and 427 cluster-last seizures.

B. Patient-specific differences in grand average REN

To understand whether there were differences in the dynamics of different seizure types as a whole, we compared the grand average REN values within each patient. To obtain the grand average REN, REN values for all pairs of electrodes and all segments within a band and period were averaged separately for each seizure. In patient 1, differences were observed in the delta, theta, beta, and gamma bands in the near-seizure period, but not during seizure, for both seizure type comparisons (Fig. 4A, Fig. 4B).

Aggregating the grand average REN comparisons from all patients showed that the majority of the differences were seen near-seizure, especially in the beta and gamma bands (Fig. 4C). Further, near-seizure grand average REN was consistently higher in the cluster seizures than isolated seizures. There were no significant differences between isolated and cluster-last seizures during the ictal period.

Interestingly, patient-specific significant differences in grand average REN were observed in six out of nine patients in at least one band, duration, and seizure type comparison. No significant differences were observed in patients 2, 3, and 4, all of whom had very few seizures of at least one type. Patient 2 had very few cluster seizures (4 non-last, 4 last), whereas patients 3 and 4 had very few isolated seizures (< 20) compared to cluster seizures (> 600; Fig. 3).

C. Prediction

Grand average REN from different bands and periods were used for prediction because they was significantly different between seizure types in a majority of patients. This resulted in 10 features for each seizure (5 bands $\times$ 2 periods). Patient 2 was excluded from the prediction analysis because they had

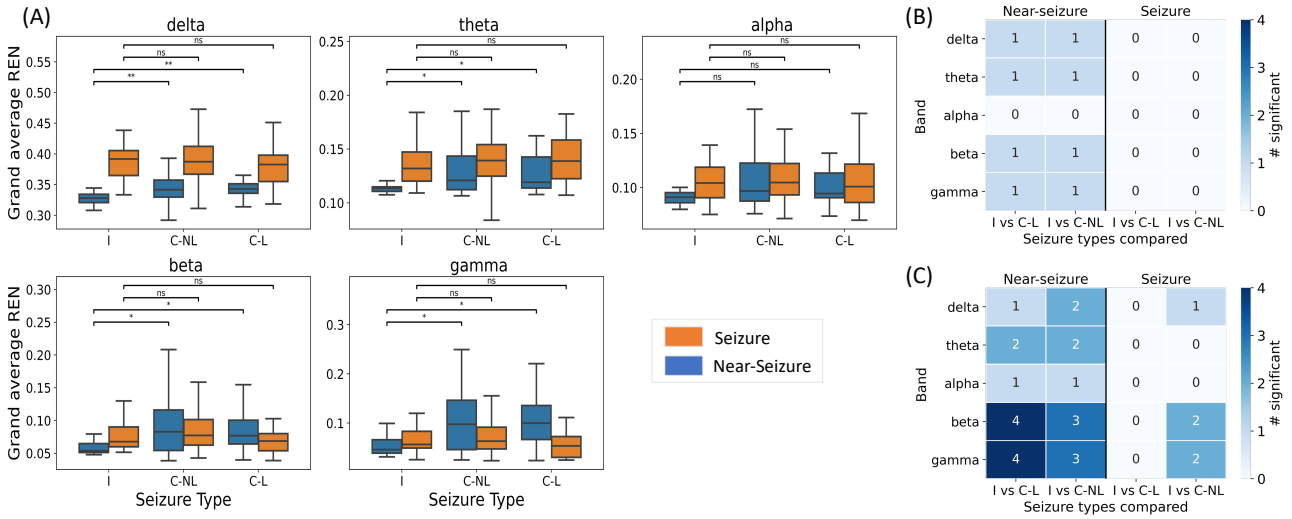

Fig. 4. Comparison of grand average REN values with a 24 hours cutoff for ISI. (A) Grand average REN values for different seizure types, bands, and periods for patient 1. Statistical comparison between different seizure types is shown during near-seizure and seizure periods (* denotes $p < 0.05$, ** denotes $p < 0.001$). FDR correction was applied for all comparisons within a patient. (B) Significant differences between grand average REN values in patient 1 represented as a heatmap. (C) Significant differences in grand average REN aggregated across patients. Annotations show the number of patients in whom there were significant differences. Abbreviations: I, isolated seizure; C-NL, cluster-non last seizure; C-L, cluster-last seizure.

TABLE I
PREDICTION PERFORMANCE FOR EACH MODEL AVERAGED ACROSS PATIENTS WITH A 24 HOURS CUTOFF FOR ISI. MEAN AND STANDARD DEVIATION (IN PARENTHESIS) OVER CROSS-VALIDATION ARE PROVIDED FOR EACH METRIC (IN %).

Model	Precision	Recall	F1-score	AUC
Log. Reg.	71.4 (22.3)	64.6 (17.6)	68.2 (16.3)	62.7 (10.1)
SVM	73.5 (32.0)	59.3 (20.6)	71.8 (16.2)	55.7 (15.7)
KNN	76.9 (28.8)	70.9 (32.4)	**73.6 (20.6)**	62.7 (7.3)
Decision Tree	70.7 (29.8)	62.7 (16.0)	64.3 (19.7)	62.5 (13.7)
Random Forest	**77.0 (29.3)**	67.9 (18.0)	73.4 (15.2)	**66.7 (11.2)**
Baseline 1	62.5 (32.6)	50.0 (0.0)	52.3 (14.6)	50.0 (0.0)
Baseline 2	62.5 (29.2)	**100.0 (0.0)**	73.0 (25.1)	- (-)

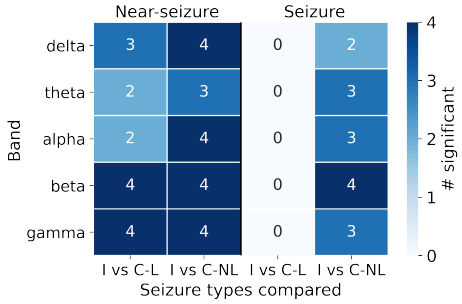

Fig. 5. Significant differences in grand average REN aggregated across patients with an 8 hours cutoff for ISI. FDR correction was applied for all comparisons within a patient. Annotations show the number of patients in whom there were significant differences. Abbreviations: I, isolated seizure; C-NL, cluster-non last seizure; C-L, cluster-last seizure.

very few cluster-non last seizures ($n = 4$, Fig. 3). On average across the remaining eight patients, random forests achieved the best prediction (Table I) with 77.0 % precision and 67.5% AUC while k-NN achieved the best F1-score of 73.6%. Performance of a majority of the prediction models was comparable or better than the baseline models. We also show the patient-specific performance for random forest because it was the best predictor in two metrics (Table II). The performance was variable across patients, ranging from $52.5\% - 95\%$ F1-score. Random forest was better than chance level predictor (baseline 1) for all the patients based on F1-score. Random forest was better than baseline 2 (that always predicts "cluster") in two patients. Although baseline 2 achieves a high F1-score for patients with a higher number of cluster seizures, it produces a considerable number of false alarms. Machine learning-based models reduce the number of false alarms, as demonstrated by their higher precision (Table II).

D. Robustness analyses

We evaluated the robustness of our results to the definition of clusters by repeating the analyses using an 8 hour cutoff for the inter-seizure interval. Overall, the results with the modified cutoff were largely consistent with the 24 hours cutoff results. There were 948 isolated clusters, 2123 cluster-non last seizures, and 639 cluster-last seizures. Grand average REN was significantly different in eight patients (Fig. 5). Majority of the differences were observed in the beta and gamma bands. There were no differences in grand average REN between isolated and cluster-last seizures during the ictal period. Random forest models were the best predictor of seizure type with 66.5% F1-score and 73.8% AUC averaged across patients (Table III). ML techniques were better than baseline predictors.

TABLE II

PATIENT-SPECIFIC PREDICTION PERFORMANCE FOR THE BEST PREDICTOR WITH A 24 HOURS CUTOFF FOR ISI. MEAN AND STANDARD DEVIATION (IN PARENTHESIS) OVER CROSS-VALIDATION IS PROVIDED FOR EACH METRIC (IN %). PATIENT 2 WAS EXCLUDED FROM PREDICTION ANALYSIS BECAUSE THEY HAD FEW CLUSTER-NON LAST SEIZURES ($n = 4$).

Patient #	Random Forest				Baseline 1				Baseline 2			
	Precision	**Recall**	**F1-score**	**AUC**	**Precision**	**Recall**	**F1-score**	**AUC**	**Precision**	**Recall**	**F1-score**	**AUC**
1	**69.1 (8.2)**	59.4 (18.6)	61.6 (9.2)	**62.1 (7.7)**	59.4	50.0	54.3	50.0	59.4	**100.0**	**74.6**	-
2	-	-	-	-	-	-	-	-	-	-	-	-
3	**97.1 (1.3)**	93.1 (2.9)	95.0 (1.8)	**79.1 (7.8)**	95.9	50.0	65.7	50.0	95.9	**100.0**	**97.9**	-
4	88.5 (3.0)	82.2 (4.9)	85.1 (1.3)	50.0 (8.0)	88.6	50.0	63.9	50.0	**88.6**	**100.0**	**94.0**	-
5	**56.8 (6.0)**	56.0 (9.5)	55.7 (5.9)	**56.0 (8.2)**	52.9	50.0	51.4	50.0	52.9	**100.0**	**69.2**	-
6	**91.3 (3.6)**	77.5 (3.2)	83.7 (2.0)	**65.4 (5.8)**	88.8	50.0	64.0	50.0	88.8	**100.0**	**94.1**	-
7	**73.3 (38.9)**	70.8 (18.2)	**78.3 (13.6)**	**82.9 (13.5)**	26.3	50.0	34.5	50.0	26.3	**100.0**	41.7	-
8	**81.7 (4.8)**	69.6 (7.0)	75.1 (6.1)	**72.7 (2.6)**	70.3	50.0	58.4	50.0	70.3	**100.0**	**82.6**	-
9	**58.0 (38.2)**	34.7 (18.5)	**52.5 (11.1)**	**65.1 (12.1)**	17.8	50.0	26.3	50.0	17.8	**100.0**	30.3	-

TABLE III

PREDICTION PERFORMANCE FOR EACH MODEL AVERAGED ACROSS PATIENTS WITH AN 8 HOURS CUTOFF FOR ISI. MEAN AND STANDARD DEVIATION (IN PARENTHESIS) OVER CROSS-VALIDATION ARE PROVIDED FOR EACH METRIC (IN %).

Model	Precision	Recall	F1-score	AUC
Log. Reg.	**71.2 (16.3)**	59.2 (21.7)	61.8 (20.6)	69.4 (6.9)
SVM	60.2 (27.8)	52.7 (31.7)	65.8 (16.6)	56.6 (21.6)
KNN	72.9 (15.2)	59.0 (26.8)	64.5 (17.3)	70.4 (10.1)
Decision Tree	61.2 (24.8)	62.5 (10.5)	60.5 (12.2)	68.9 (10.1)
Random Forest	68.3 (27.7)	63.2 (11.0)	**66.5 (15.0)**	**73.8 (9.9)**
Baseline 1	45.1 (26.3)	50.0 (0.0)	44.1 (15.0)	50.0 (0.0)
Baseline 2	45.1 (25.0)	**100.0 (0.0)**	58.6 (24.2)	- (-)

IV. RELATED WORK

We discuss related work from: (i) seizure forecasting, which tackles a similar problem of predicting the next seizure and has motivated the use of different features in our analysis; and (ii) seizure cluster detection and analyses, which have highlighted salient characteristics of cluster seizures.

A. Seizure forecasting

Seizure forecasting considers the problem of predicting the likelihood of a seizure at a given time in the future based on inter-ictal and pre-ictal data. Several techniques have been developed for seizure forecasting, ranging from traditional ML methods to more recent deep learning models [17]. Univariate, bivariate, and multivariate features extracted from inter-ictal EEG data have been used for seizure forecasting with varying degrees of success [18], [19]. Convolutional neural networks applied to EEG have been used to forecast seizures in canines and humans better than hand-crafted features combined with traditional ML methods [20], [21]. Our approach is different from the forecasting literature in the use of pre-ictal and ictal (seizure) data to predict seizures, while a majority of seizure forecasting models use inter-ictal data to forecast seizures.

B. Seizure cluster detection and comparison analyses

Previous methods have mainly addressed the detection of seizure clusters retrospectively based on inter-seizure intervals (ISI) using threshold-based methods and statistical methods [22]. Threshold based methods classify seizures with ISI less than the given threshold (for e.g., 8 hrs, 24hrs) as belonging to a cluster [6]. While these methods are easy to use, they do not account for the differences in baseline seizure rate of individuals and can be prone to false positives/negatives. On the other hand, statistical methods rely on trends in the data to identify clusters. Chiang et al. proposed a change point detection-based method that relies on seizure diaries to identify seizure clusters and identified several clusters that were missed by threshold detectors [16]. For the NeuroVista data, Seneviratne et al. visualized trends in ISI to identify seizure clusters and seizure bursts [23]. Most cluster detection methods rely on ISI for detection and are, therefore, not suitable for the proposed prediction task.

Few studies have statistically compared isolated seizures and seizure clusters to identify differences in their characteristics. Ferastraoaru et al. compared the duration of isolated and cluster seizures pooled from 92 patients and observed that isolated seizures were longer than the first seizure in a cluster and intracluster seizures, but were similar in duration to the last seizure in a cluster [6]. Karoly et al. compared isolated seizures and cluster seizures with very short ISI, termed as seizure bursts, in the NeuroVista data [7], and observed differences in the energy in the pre-ictal period of isolated seizures and burst seizures in some patients. Previous studies have not explored the individualized prediction of seizure clusters or the use of a bivariate iEEG feature for comparing seizure types.

V. CONCLUSION

We extracted a bivariate iEEG measure from long-term iEEG to discover differences in the seizure dynamics of isolated and clustered seizures and to predict seizure clustering. The dynamics for isolated and cluster seizures were different in six out of nine patients. The majority of the differences were observed in the higher frequency bands (beta and gamma) and in the pre-ictal period. ML-based patient-specific models achieved 73.6% F1-score in predicting clustering, i.e., the occurrence of another seizure shortly after a seizure, using REN. Our results can be clinically valuable in personalizing epilepsy treatment by guiding the selection of anticonvulsant drug suitable for a given seizure type. Our approach also supports the use of graph-theoretic methods [8], [24] to gain insights into how seizure progression varies for different seizure types, which can be useful in predicting seizure clusters.

Limitations and future work. There are several limitations of our study. Firstly, we used a threshold-based approach for detecting seizure clusters. It has been argued that differences in the baseline rate of seizures of individuals must be taken into account for detecting seizure clusters [16]. Secondly, seizure onset zone (SOZ) and non-SOZ electrodes have different dynamics [11] although we did not distinguish between them while averaging REN over all pairs of electrodes. Further improvements are needed in the prediction performance. ML methods that can learn complex short- and long-term relationships in REN timeseries and that pool data across patients to improve sample size may boost predictive performance.

Additional analyses is needed to make cluster prediction practically viable. Since the prediction is patient-specific, it would useful the study the effect of patients' characteristics on prediction performance. To determine the amount of data needed for each patient, it is important to investigate changes in model performance as the number of seizures used for training varies. Finally, prediction will be practically useful on lead seizures since intra-cluster seizures can be easily determined by previous seizures. Further analysis on isolated and cluster-first seizures can provide insights useful for building those models. We plan to address these directions in the future.

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