

BRIEF COMMUNICATION

Forecasting seizure clusters from chronic ambulatory electrocorticography

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Abstract

Seizure clusters are seizures that occur in rapid succession during periods of heightened seizure risk and are associated with substantial morbidity and sudden unexpected death in epilepsy. The objective of this feasibility study was to evaluate the performance of a novel seizure cluster forecasting algorithm. Chronic ambulatory electrocorticography recorded over an average of 38 months in 10 subjects with drug-resistant epilepsies was analyzed pseudoprospectively by dividing data into training (first 85%) and validation periods. For each subject, the probability of seizure clustering, derived from the Kolmogorov–Smirnov statistic using a novel algorithm, was forecasted in the validation period using individualized autoregressive models that were optimized from training data. The primary outcome of this study was the mean absolute scaled error (MASE) of 1-day horizon forecasts. From 10 subjects, 394 ± 142 (mean $\pm$ SD) electrocorticography-based seizure events were extracted for analysis, representing a span of 38 ± 27 months of recording. MASE across all subjects was $.74 \pm .09$, $.78 \pm .09$, and $.83 \pm .07$ at .5-, 1-, and 2-day horizons. The feasibility study demonstrates that seizure clusters are quasiperiodic and can be forecasted to clinically meaningful horizons. Pending validation in larger cohorts, the forecasting approach described herein may herald chronotherapy during imminent heightened seizure vulnerability.

KEYWORDS

ambulatory electrocorticography, epilepsy, forecasting, seizure clusters

1 | INTRODUCTION

Temporal analysis of chronic electrocorticography (cECoG) data has partially deconvoluted the canonical stochasticity of seizures into cycles of risk occurring at different timescales.¹ In this framework, seizures are more likely to occur when these cycles resonate to produce

periods of elevated seizure risk. Sustained elevation of risk, possibly spanning several days, accounts for seizure clusters, defined here as seizures that occur in rapid succession.² Seizure clusters are associated with treatment recalcitrance, status epilepticus, hospitalization, sudden death, and poor quality of life, thereby adversely affecting patients and their caregivers.^{3,4} Reliable seizure cluster

prediction would immensely benefit individuals with epilepsy, heralding chronotherapy during imminent heightened vulnerability to seizures.

Common definitions of seizure clusters vary: ≥ 3 seizures in 24 h ($C_{3/24}$), ≥ 2 seizures in 24 h ($C_{2/24}$), and ≥ 2 seizures in 6 h ($C_{2/6}$).³ In contrast to these ad hoc definitions, we propose a probabilistic formulation of seizure clustering (C_Φ) derived from the ubiquitous Kolmogorov–Smirnov statistic, thus accommodating all three definitions.^{5,6} We evaluate the practical performance of C_Φ in correctly classifying seizure clusters defined by the standard clinical definitions, $C_{\text{Clinical}} = \{C_{3/24}, C_{2/24}, C_{2/6}\}$. We then use C_Φ to forecast seizure clusters.

We hypothesize that the probability of seizure clustering is quasiperiodic at varying timescales. Accordingly, we forecast seizure clusters analogous to weather forecasting in which past information predicts the future. We develop individualized generalized autoregressive score models and assess their performance pseudoprospectively.⁷ Although aptly constructed clinical trials may validate our seizure cluster forecasting algorithm, they will be futile if our forecasting approach has no practical utility. Forecasting must be both accurate and timely, permitting clinically meaningful interventions. Therefore, the primary outcome of this feasibility study is forecast error at the 1-day horizon.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This single-center, retrospective feasibility study was approved by the institutional review board at the University of Alabama at Birmingham. We screened all individuals with epilepsy treated with an US Food and Drug Administration-approved closed-loop brain stimulator, hereafter referred to as "RNS" (NeuroPace) before December 31, 2017, and recruited 10 subjects.⁸ All subjects were adults (age ≥ 19 years) with at least 6 months of ECoG data and 50 electrographic seizures. Mean age was 37 ± 7 years, and four patients were female. In patients diagnosed with bilateral temporal ($n = 5$), dominant mesial temporal ($n = 3$), and unilateral frontal ($n = 2$) epilepsy, RNS was implanted into the bilateral amygdala–hippocampi (depth electrodes), combined lateral temporal lobe (subdural strip) and hippocampus (depth electrode), and peri-Rolandic region (subdural strips), respectively.

2.2 | Data selection

The RNS system is programmed to detect and archive epochs of ECoG representing sustained epileptiform

activity (i.e., suspected seizures), typically at least 15 s in duration, based on individualized detection parameters. Following RNS device implantation, patients were evaluated at the University of Alabama at Birmingham Neuromodulation Clinic.⁹ During initial clinic visits, the RNS detection parameters were optimized for seizure detection using patient-reported seizure logs (mean optimization time = 2 ± 1.5 months). These self-reported seizure logs were correlated to RNS-detected seizure ECoG events to ascertain optimal parameter selection.

For each patient, after parameter optimization, all recorded RNS ECoG epochs were visually inspected by a board certified epileptologist (S.P.) to confirm seizure activity (positive predictive value of seizure detection = 88%). Seizures were defined as epileptiform activities lasting at least 10 s in duration that evolved in space, recruiting at least two bipolar channels. The time stamps of those RNS epochs confirmed to be seizures were used to construct a time series of seizure events, E , for each subject (Figure S1). Only time stamps of observer-confirmed seizures from RNS-stored ECoG (i.e., "long episodes") were used in the analysis.

2.3 | Seizure cluster definition

The Kolmogorov–Smirnov statistic, λ , represents goodness-of-fit between an empirical and expected distribution.⁶ In particular, it can detect departure from periodicity in time series, either delayed or accelerated event arrival.¹⁰ To this end, we define a new statistic, λ^* , that has an identical cumulative distribution function to λ but quantifies whether the rate of the events is accelerated (Supplement S1). Thus, λ^* can be used as a measure of event clustering, distributed with the probability density $\Phi(\lambda^*)$. An event that occurs in rapid succession to the prior event yields a high λ^* -value, whereas an event that is delayed relative to the prior event yields a low λ^* -value.

Now we define our algorithm, C_Φ , for computing the probability of seizure clustering:

1. Select a subsequence of $n > 0$ events, E_W , contained in a time window, W ;
2. Compute λ_W^* for E_W ; and
3. Evaluate the probability, $\Phi(\lambda_W^*)$, of seizure clustering in W .

For example, the probability, p_i , that the i th individual seizure in E is clustering is obtained by segmenting E into windows containing exactly 1 seizure and computing C_Φ for each of these windows, thus yielding event probabilities of clustering. Then seizures with probabilities above a threshold, α , are classified as clustering. The probability

that a series of seizures is clustering is obtained by computing C_Φ over a window containing these seizures.

2.4 | Forecasting

We implemented a pseudoprospective trial design by dividing E into training (first 85% of data) and validation periods. We computed our algorithmic score, C_Φ , over these periods using a sliding window of fixed length τ equal to 10 times the mean interseizure interval within the training period, with 95% overlap. We used $C_{\Phi, \text{Training}}$ to optimize scale and time-lagged parameters of individualized generalized autoregressive score (GAS) models by minimizing the mean squared error between the fitted model and the training data. We then used the result to forecast $C_{\Phi, \text{Validation}}$ over .5–2.5-day horizons (Figure S1).

2.5 | Outcomes and statistical analysis

We evaluated the performance of C_Φ as a classifier for each seizure against C_{Clinical} by varying α to compute receiver operator characteristic (ROC) curves. For each subject and C_{Clinical} , the threshold that maximized correct seizure classification was then selected to compute the maximum correct classification percentage. The forecasting performance was calculated as the mean absolute scaled error (MASE) between the forecasted $C_{\Phi, \text{Forecasted}}$ and $C_{\Phi, \text{Validation}}$.¹¹ Values of MASE < 1 represent an improvement over a naïve, random walk predictor. For statistics, we computed mean and SD of C_Φ classification accuracy and forecast errors across all subjects. Additionally, we performed a sensitivity analysis by varying τ by 50% and by using 75% and 90% of E for training.

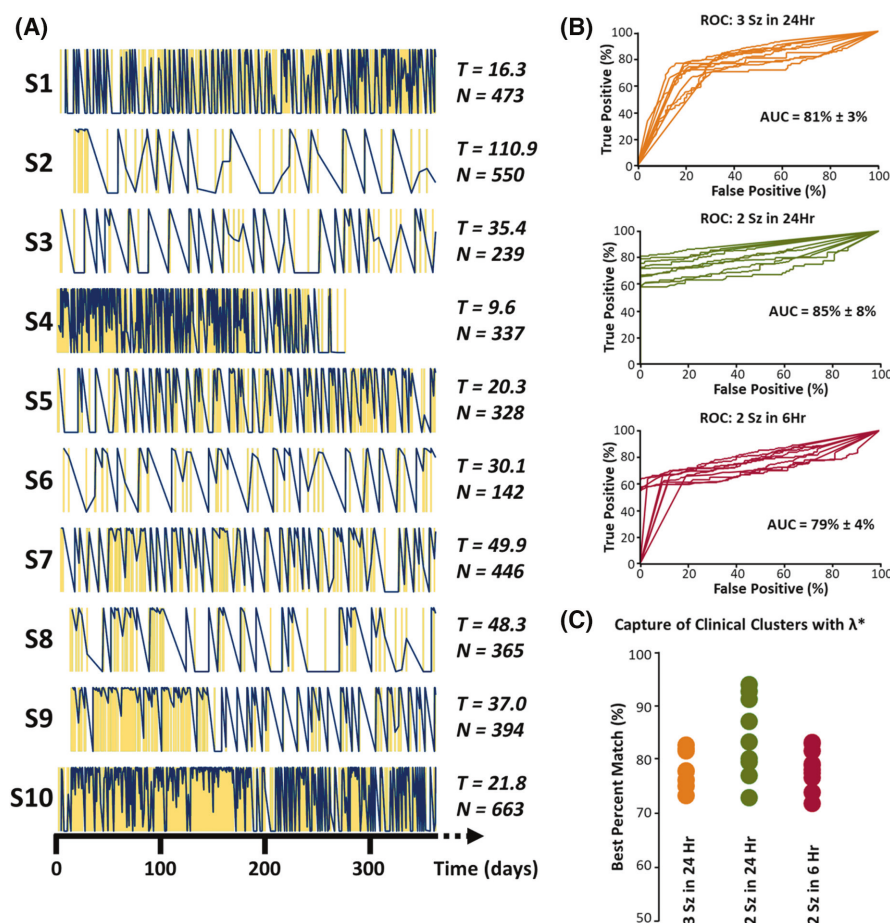


FIGURE 1 Classification of seizure clusters using λ^* versus three common clinical definitions: three seizures in 24 h ($C_{3/24}$, orange), two seizures in 24 h ($C_{2/24}$, green), and two seizures in 6 h ($C_{2/6}$, red). (A) The event probabilities of clustering calculated using $\Phi(\lambda^*)$ (blue lines) are plotted over the seizure events during the first year of analysis for each patient (yellow lines). The heights of all events are identical and represent 100% probability of clustering. Shown are the total durations of analysis, T (in months), and total number of seizure events, N , for each patient. (B) The three receive operator characteristic (ROC) curves illustrate the performance of the C_Φ algorithm compared to the standard clinical definitions, $C_{3/24}$, $C_{2/24}$, and $C_{2/6}$, in identifying seizure clustering. Areas under the curve (AUCs) are listed for each ROC curve. (C) Scatter plot showing percent correct classification of seizure clusters by λ^* with the optimal α -threshold.

3 | RESULTS

We analyzed electrographic seizures, on average 394 ± 142 per subject, over an average span of 38 ± 27 months of recording (Figure 1A). The clinical definitions identified $48\% \pm 20\%$ ($C_{3/24}$), $75\% \pm 16\%$ ($C_{2/24}$), and $47\% \pm 13\%$ ($C_{2/6}$) of seizures as parts of a seizure cluster. Using C_Φ as a seizure clustering classifier, the mean areas under the resulting ROC curves across all subjects were, respectively, $.81 \pm .03$, $.85 \pm .08$, and $.79 \pm .04$ (Figure 1B). Using the optimal α , C_Φ correctly classified $78 \pm 3\%$, $84 \pm 7\%$, and $79 \pm 4\%$ defined by C_{Clinical} (Figure 1C). MASE across all subjects was $.74 \pm .09$, $.78 \pm .09$, and $.83 \pm .07$ at .5-, 1-, and 2-day horizons (Figure 2). Individual forecasting performance results are presented in Table S1. Interestingly, in one subject (Subject 8) with catamenial epilepsy, good performance (MASE = .73) was observed. On the other hand, in subjects with improved (Subject 10) or worsened (Subject 1) seizure frequencies toward the end of the evaluation period as compared to the

beginning, performance seemed worse (MASE = .86 and .87, respectively).

4 | DISCUSSION

We define a novel, probabilistic formulation of seizure clusters, which has substantial implications for epilepsy care in intractable patients, with potential for reducing seizure-related morbidity and perhaps mortality. We demonstrate that C_Φ reliably captures clusters defined by the three common clinical definitions.³ Finally, we demonstrate the practicality of forecasting seizure clusters using individualized GAS models. We neither interpolated nor excluded missing cECoG data. Therefore, our results likely underestimate the true feasibility of seizure cluster forecasting on otherwise optimal data.

In individuals with epilepsy, mean seizure frequencies range from several per day to fewer than one per month.

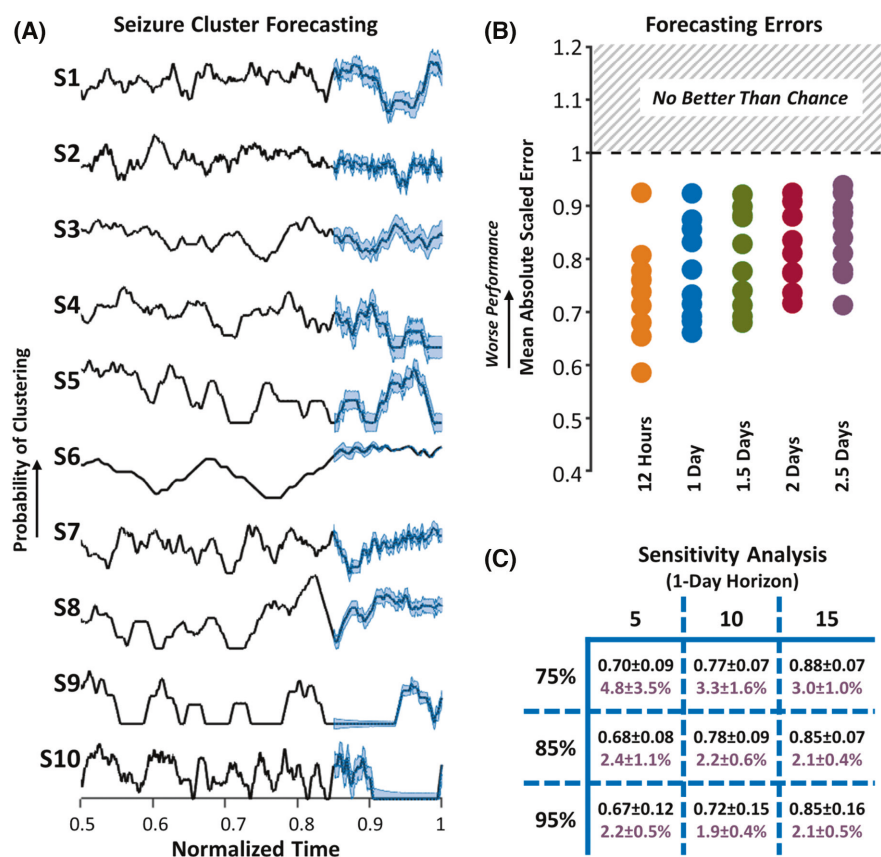


FIGURE 2 Forecasting seizure clusters. (A) Plot of seizure clustering probability over normalized time (50%–100% of data) for each patient (black lines). Using individualized generalized autoregressive score models, the forecasted clustering probabilities in the validation periods (85%–100% of data) were computed from the median of 1000 scenarios at 1-day horizons (blue dotted lines); the 2.5%–97.5% quantiles are also shown (blue patches). (B) Mean absolute scaled error (MASE) of forecasting to 2.5-day horizons. (C) Sensitivity analysis results by varying the validation period from 75% to 95% (rows) and the length of the sliding window from five to 15 times the mean interseizure interval (columns) within the training period. Shown are the mean $\pm$ SD of MASE and root-mean-square error (brown) of all subjects at 1-day horizons.

Clearly, seizures in the latter category have infinitesimal likelihood of clustering and hence the C_{Clinical} approach is not always applicable. In contrast, C_{Φ} is agnostic to an individual's typical seizure frequency and applies to any time series (Figure S1). Therefore, an analogous C_{Φ} can be computed for self-reported seizures derived from individual diaries, and the feasibility of our forecasting algorithm can also be tested on this dataset.¹²

Our seizure cluster forecasting algorithm forecasts probabilities of heightened vulnerability to 2.5-day horizons with unprecedented accuracy.^{1,13,14} This timely knowledge of impending risk permits clinicians to initiate preemptive therapies. However, individual patient sentiment may vary based upon tolerance of false positives, comfort of knowing impending cluster risk at long horizons, and other factors.¹⁵

5 | CONCLUSIONS

C_{Φ} is a promising and practical algorithm that enables forecasting seizure clusters by leveraging their natural quasiperiodicity. These forecasts accurately predict periods of heightened vulnerability to seizures at least 24 h in advance and will form the foundation for future validation studies on larger cECOG and self-reported datasets. Given the small sample size here, further validation in a larger prospective cohort is the next step in disseminating utility to the epilepsy community.

AUTHOR CONTRIBUTIONS

Conception and design: Adeel Ilyas, Yuri Dabaghian, Samden D. Lhatoo, Sandipan Pati. Acquisition and data analysis: Adeel Ilyas, Clarissa Hoffman, Yash Vakilna, Sreekanth Chaliyeduth, Wolfgang Muhlhofer, Kristen O. Riley, Yuri Dabaghian, Sandipan Pati. Drafting the manuscript: Adeel Ilyas, Samden D. Lhatoo, Sandipan Pati.

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CONFLICT OF INTEREST

S.P. has received honoraria from NeuroPace for consulting; however, he declares no targeted funding or compensation from NeuroPace for this study. The remaining authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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