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Extreme events in epilepsy

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***Abstract*—In this paper, we aim to provide a brief review of the research of epileptic extreme events. The main topics of interest include extreme value theory approaches used to describe mechanisms in the epileptic brain and to detect/predict seizures as well as possible applications of the results obtained in medical diagnostics. The main purpose of the review is to draw attention to this relevant area of research.**

***Index Terms*—extreme value theory, heavy-tailed distribution, epilepsy, electroencephalogram**

I. Introduction

Extreme events are rare abnormal deviations in system behavior from a typical state [1], [2]. Existing results support the fundamental nature of this phenomenon and the presence of extreme events in wide variety of dynamical systems. Extreme behavior was throughly studied in model systems such as coupled oscillators and complex networks [1], [3], [4]. Various scenarios for the occurrence of extreme events have been shown in physical experiments with fluids [5] and nanophotonic and optical systems [6]–[8]. In everyday life extreme events are associated with sudden changes in climate [9], [10], rogue waves in the ocean [11], financial crises [12], traffic jams [13], etc. Such events are potentially harmful, thus they are studied in depth. Research of extreme behavior can provide insight into the hidden mechanisms that drive the system to this unwanted state, which can help with detection and prediction of these events [14], [15]. Extreme events are often associated with critical behaviours that are accompanied by different types of intermittency [16]–[19], which is also one of the signs of extreme behaviours.

The great diversity of manifestations of extreme events allows us to expect the presence of extreme dynamics in living systems. Indeed, power distributions in biomedical data are often “skewed” and demonstrate “heavy” tails. According to the fundamentals of extreme value theory [20], [21], such behavior marks the presence of extreme dynamics in the system. Extreme fluctuations of health parameters can be linked to some unusual processes, that affects the normal dynamics of the system and possibly lead to acute crisis. Thus, research on extreme events is especially relevant in medicine, where detection and prediction of such events can benefit medical diagnostics and treatment as well as provide insight into mechanisms of the disorder.

Epilepsy is one the brightest examples of extreme dynamics in living systems, and it can benefit greatly from implementation of extreme value theory. On the one hand, the rapid development of epileptic seizures, involving the sudden synchronization of billions of neurons, exhibits dynamics similar to extreme. Their dynamics also have some properties of on-off intermittency [22], [23]. This is in line with fundamental principles of extreme event generation in a “small-world” network [24]. Thus, it can be possible to describe the mechanisms governing the generation of epileptic seizures by considering neuron-based mathematical models.

On the other hand, epilepsy is a dangerous neurological disorder in need of treatment [25]. Seizures are commonly controlled with drugs [26], surgery [27] of neurostimulation [28], however, regardless of the treatment the diagnostics is crucial. In this context, extreme value theory can compliment both traditional methods of spectral analysis and advanced approaches of machine learning in developing fields of early diagnostics and seizure prediction [29], [30].

In this paper, we aim to provide a brief review of this area of research. The main topics of interest include extreme value theory approaches used to describe mechanisms in the epileptic brain and to detect/predict seizures as well as possible applications of the results obtained in medical diagnostics. The main purpose of the review is to draw attention to this relevant area of research.

II. Epileptic seizures as extreme events in EEG

The concept of epileptic seizures as extreme events has been known for some time [31]. While these extreme events were understudied and underrepresented for some time, they have recently received considerable attention [32]. There were several important papers in this area of research.

Pisarchik et al. [33] studied electroencephalogram (EEG) of mice after induced ischemic stroke, that demonstrated so-called post-stroke seizures [35]. The authors used continuous wavelet transform (CWT) with Morlet mother wavelet [36] to investigate the time-frequency structure of EEG signals associated with normal activity and extreme events. As the main CWT-based feature, they considered the wavelet energy W in the frequency range $f \in [1, 30]$ Hz and normalized it to the maximum energy in this range. To analyze extreme dynamics, the authors implemented extreme value theory (EVT). They constructed PDFs of W and tried to fit them with certain theoretical distributions. The PDF of normal, non-seizure activity was perfectly fitted by the Weibull distribution,

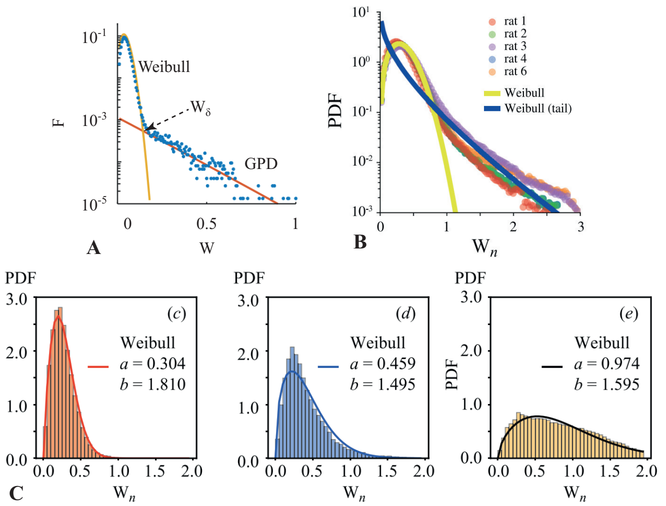

Fig. 1. Distributions of wavelet energy. (A) PDF for the frequency band $\sim$ 20 Hz for post-stroke mice. Blue dots correspond to the empirical PDF $F(W)$. Yellow curve is the Weibull distribution that fits the non-extreme part of $F(W)$, and red line is the GPD fitting the extreme part. The threshold W_δ between them is indicated by an arrow. (B) PDF for the frequency band $\sim$ 7 Hz for WAG/Rij rats. Colored circles correspond to experimental PDFs obtained from the data of five WAG/Rij rats. Curves are Weibulls with different parameters well-fitted to normal activity (yellow) and heavy tail (dark blue); (C) PDFs for the frequency band $\sim$ 7 Hz for WAG/Rij rats. PDFs are histograms and fitted Weibull distributions are curves for different segments of the EEG close to seizure onset: far from the onset, before the onset, during the seizure. Based on materials from Pisarchik et al. [33], Frolov et al. [34].

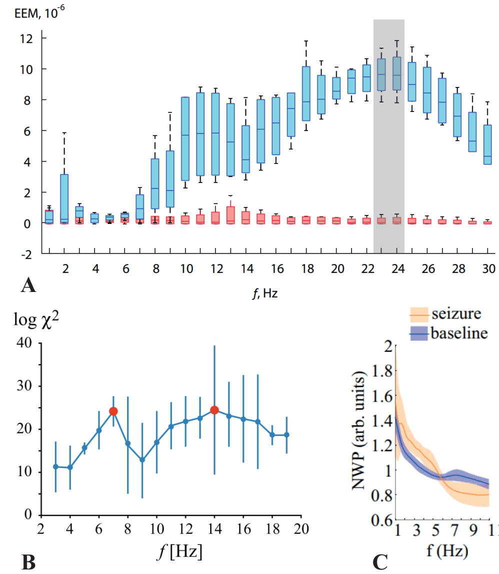

Fig. 2. Localization of epileptic extreme dynamics in frequency domain. (A) Box-and-whisker plot of EEM versus frequency for 6 healthy mice (colored in red) and 6 post-stroke mice (colored in blue). The grey rectangle indicates the frequency band with the most extreme brain behavior. (B) Semi-log dependence of Pearson's chi-squared statistic χ^2 on oscillation frequency. Here χ^2 quantifies the difference between normal and epileptic PDFs. Red dots indicate the components with maximum χ^2 values and thus the most pronounced extreme behavior. (C) Wavelet energy corresponding to the epileptic seizure and the baseline. Data are presented as group means $\pm$ standard error. Based on materials from Pisarchik et al. [33], Frolov et al. [34], Karpov et al. [38].

while the PDF for seizures was modeled by the generalized Pareto distribution (GPD) [37]. This result is illustrated in Fig. 1 A. The authors concluded, that this marked the presence of "heavy" tail of extreme values in distribution according to the Pickands–Balkema–de Haan theorem [21]. However, this was true only for a narrow frequency band of $f \in [22, 24]$ Hz related to epileptic seizures in EEG. Thus, extreme events showed a sharp, sudden increase in the wavelet energy in epileptic frequency range, while the energy in other ranges remained unchanged. Based on this findings, the authors developed a novel approach to detecting and quantifying extreme events in EEG. They introduced extreme event measure (EEM) designed to assess heaviness of PDF tail by contrasting it to Weibull distribution. Using this technique, the authors showed the difference between healthy and stroke mice, suggesting that the proposed method can be used to epileptic seizure detection. Fig. 2 A demonstrates the comparison of EEM between healthy and stroke mice with maximum difference in mentioned frequency band of $f \in [22, 24]$.

Frolov et al. [34] continued the research by studying EEG of WAG/Rij rats with genetic predisposition to absence epilepsy [39]. Like Pisarchik et al. [33], the authors used CWT to describe time-frequency features of the EEG and calculated the normalized wavelet energy W_n. The following analysis was also similar: PDFs were constructed for both normal and epileptic EEG and fitted by Weibull distributions with different parameters. Fig. 1 B illustrates such a fit — one can see that Weibull drastically changes form between normal and epileptic data. Once again, the analysis revealed "heavy" tail related to the presence of extreme events in EEG, and the effect was found in frequency range of epileptic seizure of WAG/Rij rats ($f \in [6, 9]$ Hz) as well as its harmonic ($f \in [12, 18]$ Hz). For details see Fig. 2 B. This results support the claim by Pisarchik et al. [33] that epileptic seizures are extreme events in certain frequency range of EEG.

The authors also addressed the predictability of epileptic seizures. They considered time intervals between seizures (return times) and fitted their PDF by a power-law distribution with power $-3/2$. This is in good agreement with previously reported intermittent behavior in the epileptic brain [23], [40] and suggests the presence of long-range correlations in epileptic EEG. To prove this hypothesis, the authors implemented detrended fluctuation analysis (DFA) [41] to study the wavelet energy at different frequencies. They demonstrated DFA exponent > 0.9 for 7 Hz and 14 Hz oscillations, which suggests a highly structural and self-organized behavior, that possibly can be predicted. To test this suggestion, the authors considered several time intervals in the transition from normal to epileptic EEG. PDF of wavelet energy in 7 Hz range gradually changes it shape as it approaches the onset of the seizure. PDFs at different intervals were fitted by Weibulls with different parameters, and the authors concluded, that changes in these parameters can be used to predict epileptic seizures 1–7 s before the onset. Examples of such PDFs and fitted Weibulls are shown in Fig. 1 C.

Karpov et al. [38] tested plausibility of previous findings on human data. The authors analyzed EEG data collected during long-term monitoring of patients with focal epilepsy. CWT-based analysis included calculation of wavelet energy in two frequency ranges: 1–5 Hz and 5–10 Hz. The authors showed, that the lower frequency range corresponds to epileptic extreme events in human EEG. For reference, see the wavelet spectra of normal and epileptic EEG in Fig. 2 C. The authors used wavelet energy averaged over 1–5 Hz range to construct PDFs in baseline and seizure. Like Frolov et al. [34], they fitted PDFs with Weibulls, whose parameters significantly differed between baseline and seizure. However, only the Weibull for seizures was "heavy"-tailed, showing signs of extreme behavior.

Additionally, the authors speculated about possible mechanisms of seizure emergence. Based on the findings by Frolov et al. [34], they suggested a scenario in which epileptic extreme events occur due to instability and are preceded by noise amplification. To test this hypothesis, the authors estimated noise intensity and signal variance in several time windows and showed that both these characteristics gradually increased as seizure onset approached.

In their follow-up paper [42] Karpov et al. explored applications of EVT in seizure detection. They averaged wavelet energy over characteristic to epileptic seizure ranges in spatial, time and frequency domains, and PDF for such an averaged energy demonstrated a "heavy" tail. The authors speculated that epileptic extreme events are outliers in EEG, thus special outlier detection techniques can be used to detect seizures as well. The authors proposed a one-class support vector machine (SVM) with averaged wavelet energy values as features. They tested it on clinic EEG data and achieved up to 77% in recall and 13% in precision. Given the decent recall and low precision, the authors suggested to use this approach as a Clinical Decision Support System (CDSS), which flags possible seizures and leaves the final decision to a human. They also supposed, that the presence of extreme dynamics in data is crucial for good performance of such outlier detection methods. Later, Karpov et al. experimented with various machine learning algorithms and features to improve the quality of seizure detection [43], [44].

Interestingly, research by Luca et al. [45] is in line with the previously mentioned studies, despite the fact that the authors analyzed motor activity in children with epilepsy instead of EEG. They introduced a novelty detection approach based on Weibull and Gumbel models and SVM classifier. They used it to detect seizures in acceleration data collected by 3D acceleration sensors and achieved $\sim$ 80% in sensitivity and $\sim$ 89% in precision. This approach shares certain similarities with the one proposed in Refs. [42], [46]. The results are curious, since hypermotor activity during seizures is commonly considered to be disruptive, whereas in [45] it served as marker of epileptic extreme events and was used for seizure detection. This raises an interesting topic — in biomedical data analysis, extreme events are often considered in the context of outliers, that are inconsistent with other measurements. It is commonly assumed, that outliers occur due to artifacts, external noise or measurement errors, and therefore lack any meaningful information. However, the findings by Luca et al. suggest, that such "parasitic" outliers can be linked to "inherent" extreme events, that reflect features of the data. These two types of dynamics can mix together, and their combined analysis can be a promising approach.

III. Conclusion

In this paper, we provided a brief review of the research of epileptic extreme events. The reviewed papers demonstrate that EVT can be used not only in purely applied areas of diagnostics and seizure detection/prediction, but also to gain insight into fundamental mechanisms in epileptic brain. Furthermore, these studies show that EVT can be successfully combined with other approaches such as traditional spectral analysis and advanced machine learning. We believe that future research on epilepsy could benefit from adopting this approach.

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