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Extreme events in biomedical data

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Abstract In this paper, we provided a brief review of the study of extreme events in biomedical data. The main topics of interest were states in the living system that lead to the occurrence of extreme events, types of biomedical signals containing extreme events, extreme value theory approaches used to detect/predict extreme dynamics, the results obtained and their possible application in medical diagnostics/treatment. The main purpose of the review is to draw attention to this relevant area of research.

1 Introduction

Extreme events are very rare abnormal deviations of system behaviour from a typical state [1–3]. The results of many studies support the existence of this fundamental phenomenon in a wide range of systems. Extreme events have been discovered and extensively studied in deterministic and stochastic model systems, including coupled oscillators and complex networks [1, 4–6]. Different scenarios for the emergence of extreme events have been demonstrated in physical experiments with fluids [7], nanophotonic and optical systems [8–11], etc. In real-world systems, extreme events are associated with sudden changes in climate systems [12–15], rogue waves in the ocean [16, 17], financial crises [18–20], traffic jams and monster blackouts in power grids [21], social media events [22, 23], etc. Such events are potentially harmful to human life, health and well-being, and are, therefore, studied in depth. A more pragmatic direction of research involves the development of approaches for predicting extreme events [24–26]. However, extreme value theory can also provide insight into the hidden mechanisms that drive the system to this state [27].

The great diversity of extreme events and their underlying mechanisms allows us to expect the occurrence of such events in living systems. This is particularly important in the context of medicine, since the presence of extreme events can be linked to an unusual state of the living system, or even to a disorder, that affects the normal dynamics of the system and, consequently, the recorded biomedical data. Thus, research into the detection/prediction of extreme events, as well as the mechanisms underlying their occurrence, could benefit medical diagnostics and treatment.

In biomedical data analysis, extreme events are often considered in the context of outliers—the data that are inconsistent with other measurements. Outliers can bias location and scale estimators (e.g. mean and covariance matrix) towards them, and thus affect the results of data analysis. Outliers are found in electrocardiogram (ECG) [28], electromyogram (EMG) [29], electroencephalogram (EEG) [30], etc. It is generally assumed that outliers are due to artefacts, external noise or measurement errors, and therefore do not contain any meaningful information. All this leads to the belief that outliers should be removed as part of data pre-processing. However, there is evidence that outliers can be caused by some intrinsic features of the data. For example, in ECG, some outliers are related to ectopic heartbeats, where some beats are missing or skipped for no clear reason and the heartbeat is otherwise normal [31]. In this particular case, such outliers hinder data processing as much as any other, but it raises an interesting issue: could “intrinsic” outliers possess significant information that provides insight into the state of the system? In this context, outliers in medical data are in line with the extreme events in other systems described above. Extreme events in living systems have recently received considerable attention [32], but they remain understudied and underrepresented in research.

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The main objective of this work is to provide a brief review of the study of extreme events in biomedical data. The main topics of interest are:

- states in the living system that lead to the occurrence of extreme events;
- types of biomedical signals that contain extreme events;
- extreme value theory approaches used to detect/predict extreme dynamics;
- results obtained and their possible application in medical diagnostics/treatment.

The review is not intended to be exhaustive, but mainly to draw attention to this relevant area of research. The structure of the review is as follows. Section 2 provides basic information on extreme value statistics. Section 3 discusses the application of extreme value theory to the analysis of dynamics in living systems, as well as some applications of this approach to diagnostics and crisis prediction. Section 4 is dedicated to applied novelty detection methods, which are often used to detect individual extreme events in biomedical data. In Sect. 5, we consider one of the brightest examples of extreme dynamics in living systems—epileptic activity. We discuss recent research in this area, both for applied tasks of seizure detection/prediction and for fundamental studies of the epileptic brain.

2 Extreme value statistics

One way of describing extreme events and their dynamics is through statistics [3]. From this perspective, extreme events occur in the tails of probability distributions that define the occurrence of events of a given size (in terms of energy, duration, etc.). For many systems, these distributions are close to Gaussian, and the tails to the left and right of the peak are exponential. For extreme events, however, the tails are "heavy" and are described, for example, by a power law: $p(x) \sim x^{\alpha}$, $\alpha > 0$. Power laws tend to fall off much more slowly than exponential distributions, indicating an increased probability of occurrence for events in the tails.

Extreme value theory (EVT) provides a more rigorous representation of the tails. Consider a set of m independent and identically distributed (IID) random variables $Z_m = \{z_1, z_2, ..., z_m\}$, $z_i \in R$ from a distribution function D and introduce the largest element observed in m samples as $x_m = max(Z_m)$. Fisher and Tippett [33] showed that the limit form of the probability of observing the extremum $x_m \leq x$ is given by generalised extreme value (GEV) distribution:

$$H_{GEV}(y_m, \gamma) = exp\{-[1 + \gamma y_m]^{-1/\gamma}\}, \tag{1}$$

where $\gamma \in R^{+}$ is the shape parameter and y_m is the reduced variate:

$$y_m = \sigma_m^{-1}(x_m - \mu_m) \tag{2}$$

with norming parameters σ_m and μ_m.

As $m \to \infty$, the distribution of maxima from any D converges to one of three limit forms: the Gumbel, Frechet, or Weibull distribution [34]. This is known as the Fisher–Tippett–Gnedenko theorem [35].

In a similar way, Balkema and de Haan [36] showed that the tail of the empirical probability distribution function (PDF) $F(z_i)$ (z_i exceeds the threshold z_δ) is modelled by the generalised Pareto distribution (GPD) [37]:

$$F_{GPD}(z_i|k, \sigma, \theta) = \frac{1}{\sigma}\left(1 + k\frac{z_i - \theta}{\sigma}\right)^{-1-\frac{1}{k}}, \tag{3}$$

where k, σ, θ are the GPD parameters optimised to fit the exceeding tail of empirical PDF $F(z_i)$. This is known as the Pickands–Balkema–de Haan theorem [36].

3 Extreme value dynamics

The presence of extreme events in biomedical data is expected since their power distributions are often skewed and have "heavy" tails. Such tails mark the presence of extreme dynamics in the system [35, 36], and it is widely accepted that extreme fluctuations of health parameters may trigger (or be the consequence of) some unusual and irreversible processes leading to acute crisis. In this context, the application of EVT to biomedical data could provide the probability of observing extremely low/high fluctuations of health parameters, given that the variables analysed are IID.

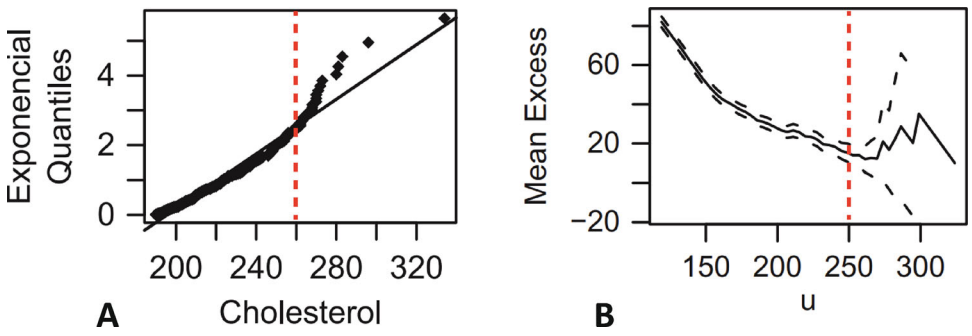

Fig. 1 Examples of exponential QQ plot for data exceeding the reference value of 190 mg/dL (**A**) and estimated mean excess function for the same data (**B**). The red dashed line marks the threshold. Based on materials from de Zea Bermudez and Mendes [38]

A straightforward implementation of this approach suggests modelling the data using EVT to assess the extreme quantile that ultimately serves as the threshold separating normality from pathology. A good example of such a study is the work of de Zea Bermudez and Mendes on high cholesterol levels in Portugal [38]. According to the World Health Organisation, hypercholesterolaemia (high cholesterol) is a risk factor for ischaemic heart disease and stroke, a reliable criterion for hypercholesterolaemia is, therefore, needed. The authors claim that studies in this area tend to describe the mean behaviour of individuals and are unable to characterise individuals with very high levels of total cholesterol. As with many other biomedical data, the normal distribution model can fit the central part of the distribution very well, but becomes completely inadequate in the tail.

The authors implemented EVT, namely the well-known peaks over threshold (POT) approach [39], which fits the exceedances above a high threshold with GPD. To assess the heaviness of the tail, they plotted the exponential quantile–quantile plots (QQ plots), which are commonly used to compare two probability distributions by plotting their quantiles against each other. Let $\{x_1, x_2, ..., x_n\}$ be an observed sample of size n and $\{x_{1:n}, x_{2:n}, ..., x_{n:n}\}$ be the corresponding ascending ordered sample. If the tail of the underlying distribution fits the exponential distribution, then the plot of the pairs $(x_{i:n}, -\log(1 - p_{i:n}))$, where $p_{i:n} = \frac{i}{n+1}$ and $i = 1, 2, ..., n$, should be linear. Otherwise, the data are heavier tailed (lighter tailed) than the exponential distribution. An example of such a QQ plot is shown in Fig. 1 A. To choose an appropriate threshold u, above which the data are confident to follow a GPD, the authors plotted the empirical mean excess function (MEF) $e(u)$. For GPD, the MEF is defined as:

$$e(u) = \frac{\sigma}{1-k} + u\frac{k}{1-k}, \tag{4}$$

where k and σ are the shape and scale parameters ($k < 1$, $\sigma + ku > 0$). If the underlying distribution is heavy-tailed, then the line $e(u)$ should increase for all higher thresholds above a certain u. An example of such a MEF is shown in Fig. 1 B. By combining these techniques, the authors were able to provide accurate estimates of high levels of total cholesterol.

However, the implementation of EVT is not always so straightforward, which is often related to the fact that the data studied are not IID. Such a case is explicitly described in the work of Faranda [40], where the author used EVT to analyse blood pressure data. This study is important in the context of cardiovascular disease research, as sufficiently large blood pressure fluctuations can trigger acute hypotensive/hypertensive episodes, which sometimes lead to cardiac crises. The author points out that blood pressure data have internal correlations due to quasiperiodic processes linked to the circulation. Therefore, some methods are needed to preserve the inherent dynamic information. According to the author, several approaches are used, including averaging of blood pressure data [41], neural networks [42], or spectral techniques [43]. All these techniques are based on the identification of a single threshold, similar to a previously mentioned work [38]. In turn, the author proposed an approach to inspect the bulk statistics, which provides a global map of the patient's status with respect to a time scale.

The author introduced recurrences in blood pressure data $p(t)$ through a time window approach. The recurrence was defined as the nearest value of p^* in the interval τ, formally $min(dist(p(t), p^*))$ for $t^* < t < t^* + \tau$. To construct the statistics of such recurrences, one should extract n values in all intervals of length τ. For details, see Fig. 2 A.

In the limit of $n, \tau \to \infty$, a series of minima

$$X_i = min(g(dist(p(t), p^*))), \; t_i < t < t_i + \tau \tag{5}$$

with a generic observable function $g(\cdot)$, will obey GEV distribution [44]. Known results [45] suggest using $g(\cdot) = -\log(\cdot)$ as it ensures correct sampling of so-called short returns and turns GEV into a Gumbel law.

In the context of the blood pressure study, the author fitted X_i to the GEV model and checked the goodness of the Gumbel model. The fit was successful if there were enough recurrences of p^* in the interval τ, otherwise it

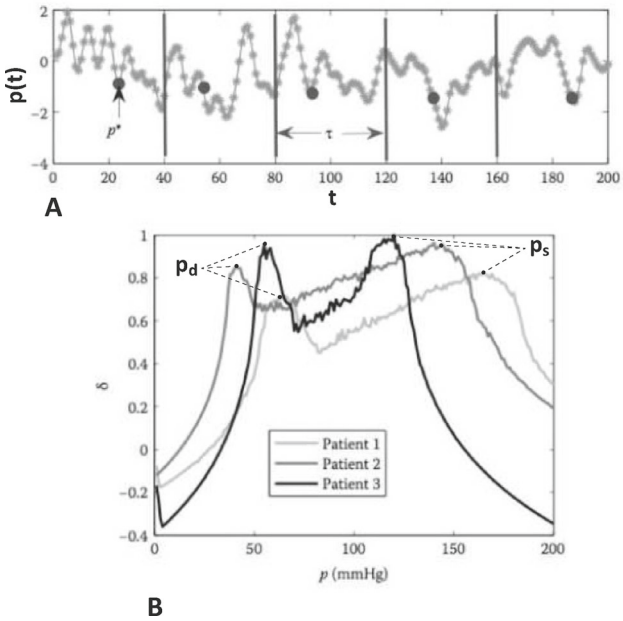

Fig. 2 **A** Recurrence based on the time window approach: recurrences are sampled over a time interval τ, as the values closest to p^* are measured in each interval. **B** Normalised likelihood of the Gumbel distribution δ for three different patients. p_s and p_d mark the systolic and diastolic pressures, respectively. Based on materials from Faranda [40]

failed. The distance between the Gumbel law and the histogram from the data was expressed as the normalised likelihood δ. The analysis was repeated to include all p^* in the range $min(p) < p^* < max(p)$. The author suggested analysing the distribution $\delta(p)$ using systolic (p_s) and diastolic (p_d) pressures as reference points [46]. The shape of the distribution can be assessed and related to the patient's condition, for example, a large range of fluctuations around p_s indicates hypertensive risk (see Patient 2 in Fig. 2B).

So far, extreme events in biomedical data have only been discussed in the context of various risks, but the situation becomes more complicated in the case of neural oscillations. Heavy tails can reflect moments of increased synchronised activity, which are associated not only with the emergence of pathological activity, but also mark the states of optimal neural processing [47]. Thus, it is believed that extreme events correspond to moments of cognitive impairment or neural dysfunction as well as to moments of intense cognitive processing or heightened attention [48]. For example, some studies report that the distributions change (e.g. become heavier tailed) in clinical conditions [49, 50], whilst others point to similar changes in the transition between normal states (eyes open/eyes closed) [51]. One possible mechanism responsible for heavy tails in skewed distributions is the presence of long-range synchronised neural activity, which may be crucial for both cognitive processes and pathological states [52, 53]. In summary, extreme events in neurophysiological data provide valuable insights into the dynamic nature of neural oscillations, and can potentially help both in understanding cognitive processes and in identifying pathological conditions.

The study by Liaqat [54] is a vivid example of the concept described. The author noted that temporal variability has often been ignored or treated as noise in neurophysiology and therefore dismissed [55]. However, studies report that there are links between such variability and various cognitive, behavioural and sensory processes—namely, higher variability may be associated with maintaining optimal performance [56]. This is consistent with the points made above and in the Introduction. The author used this basis to find biomarkers of ageing based on temporal variability of neurophysiological data.

The author considered resting-state magnetoencephalography (MEG) collected from 646 healthy ageing adults aged 18–89, representing 5 age categories of the adult lifespan. According to a review [48], both structural and neurophysiological parameters follow a skewed distribution at all levels of the brain hierarchy. The author, therefore, compared different probability distribution models to see which could accurately describe the temporal variability of neurophysiological signals. They tested 72 models on MEG data in 5 frequency ranges (delta, theta, alpha, beta and lower gamma) for both men and women of 3 age groups (younger, middle-aged and older adults). The author showed that two particular models—Generalised Gamma and Exponentiated Weibull—provided the best fit regardless of frequency range, sex and age. In light of this result, and based on the Fisher–Tippett–Gnedenko theorem, the author suggested that EVT may provide a more sensitive framework for distinguishing between neural states or for predicting clinical, behavioural or cognitive measures from neurophysiological signals.

The author then assessed extreme behaviour through the heaviness of the tails in the distributions. To do this, they constructed power probability distributions for MEG signals and analysed their two important characteristics: skewness and kurtosis. They looked at differences across five age groups, separately for skewness and kurtosis, and separately for five canonical frequency bands considered previously. To test for differences between age groups,

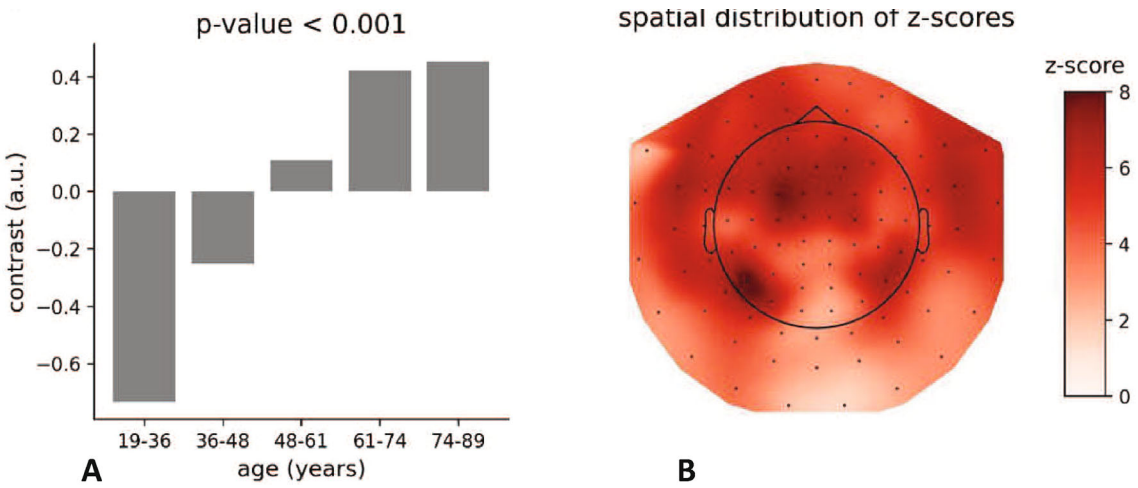

Fig. 3 **A** Data-driven overall contrast across age groups for kurtosis in the alpha band. **B** Spatial distribution of z-scores across MEG channels. Each z-score is associated with one MEG channel, demonstrating the robustness of the contribution of individual MEG channels to the overall contrast. Based on materials from Liaqat [54]

the author used a multivariate analysis known as Partial Least Squares (PLS). The results obtained suggested that estimated extreme events had distinct patterns of change across the lifespan in each frequency band, as well as unique spatial distributions of changes across brain regions. For details, see the example of kurtosis in the alpha band in Fig. 3. The author concluded that deviations from typical oscillations are involved in ageing brain processing, and should be considered as a meaningful biomarker of cognitive ageing due to the distinct trajectories of these deviations across age.

These results are particularly interesting as they are consistent with other studies exploring the concepts of criticality and quasicriticality. The hypothesis of criticality in the brain suggests that information processing occurs near a phase transition point between synchronous and asynchronous or regular and irregular states [57]. The brain can switch rapidly between these states, and small bursts of neurodynamic activity can lead to extreme events. This concept not only addresses the presence of extreme events in neurophysiological data, but also claims that neural networks must be critical to achieve optimal information transfer. This may have some clinical implications [58]. Quasicriticality suggests that the brain operates near a state of maximum dynamic susceptibility, and reaches a critical point for optimal information processing only in the absence of stimuli, noise or dissipation [59]. Successful neuronal activation occurs through neuronal avalanches whose size and duration follow scale-free or power-law distributions. Thus, both the concepts of criticality and quasicriticality contribute to the understanding of the link between extreme behaviour and fundamental brain mechanisms.

4 Novelty detection

Note that the studies discussed in Sect. 3 have focussed on the extreme dynamics of the system in general. Statistics may be sufficient to characterise the living system as a whole, but sometimes it is more appealing to study the manifestations of individual extreme events, for example, when such an event corresponds to a particularly impactful or dangerous episode such as a seizure. In this context, the task of extreme event detection becomes essential and is closely related to novelty detection methods [60].

Novelty (outlier, abnormality) detection arises when the usual assumption for supervised classification, that the data set contains information about all classification hypotheses, fails. In biomedical data, this assumption is often violated due to class imbalance, where there are very few examples of an important class within the data set. This is common in rare condition monitoring, where examples of the "normal" class are much easier and less costly to obtain than "abnormal" ones. In a decision-making system, it becomes increasingly difficult to make decisions in this class as the number of examples decreases. In such a case, it is more appropriate to build a model of the "normal" data and test for "novel" data against that model. There are certain approaches to this task that typically use a semi-parametric representation, such as a Gaussian mixture model (GMM), against which the data are assessed [61]. However, EVT provides an analytical approach to extreme event statistics [62].

Roberts [60, 62] actively developed a novelty detection approach based on EVT and GMM. Continuing the considerations started in Sect. 2, consider the Gumbel distribution in the limit $\gamma \to 0$. The probability of observing

some extremum $x_m \leq x$ is given by

$$P(x_m \leq x|\mu_m, \sigma_m) = exp\{-exp(-y_m)\} \tag{6}$$

The associated density function is:

$$p(x_m = x|\mu_m, \sigma_m) = \frac{1}{\sigma_m} exp\{-y_m - exp(-y_m)\} \tag{7}$$

For simplicity, we denote $P(x_m \leq x|\mu_m, \sigma_m) = P(x|m)$ and the corresponding density as $p(x—m)$. Thus, $P(x—m)$ can be thought of as a novelty probability, since it answers the ultimate question: whether an observed point lies outside even the expected extreme value distribution.

The GMM is widely used in data density estimation. Its form is simple and consists of $k = 1..K$ components, each of which has a standard Gaussian form and is uniquely parameterised by its mean and covariance matrix. For such a set, the data likelihood $p(x)$ can be expressed as a mixture of the component likelihoods:

$$p(x) = \sum_k \pi(k) p(x|k), \tag{8}$$

where $\pi(k)$ are the component priors. We can expect the statistics of outlying events to be dominated by k^*, the component closest to x. Thus, we are interested in the probability of data being within a certain distance h from the component mean. Integrating the density function gives:

$$P(h(x)) = \int_{c_k^*}^{h(x)} p(w|k^*) dw, \tag{9}$$

where c_k^* is the mean of the closest component and w is a variable of integration. For more complex case where x is multidimensional, Eq. (9) transforms to:

$$P(h(x)) = erf\left(\frac{h(x)}{\sqrt{2}}\right), \tag{10}$$

where $erf(\cdot)$ is the error function.

The distribution from Eq. (6) can be used as $h(x)$. In addition, if m points are used to fit the model, then the effective number of points "seen" by each component is $m_k = m\pi(k)$. Thus, the resultant EVT probability at some point x can be expressed as:

$$P(x|m) = \sum_k P(h(x)_k|m_k) p(k|x), \tag{11}$$

where $p(k—x)$ is the posterior probability of the kth Gaussian in the mixture given x. We are interested in extremal points, so we assume that all posteriors but one are close to zero. For this, one posterior k^* $p(k^*|x) \approx 1$, and this assumption can be used to simplify Eq. (11):

$$P(x|m) \approx P(h(x)_{k^*}|m_{k^*}) \tag{12}$$

Roberts also considered several examples of the implementation of the proposed approach. First, they tested an epileptic dataset consisting of a single EEG channel from an epileptic patient. The task was standard for this type of data: to detect epileptic seizures. The author used a 10-min seizure-free portion of the data to fit a GMM and then tested the rest of the data against this model. The resultant novelty probabilities can be seen in Fig. 4. In fact, the approach was able to highlight all four epileptic episodes present in the dataset (see Fig. 4A). The time series for the first episode detected (Fig. 4B) shows a 3 Hz spike-wave discharge characteristic of an epileptic seizure.

Second, the author looked at vigilance data from human subjects performing a tracking task. The data were a single EEG channel, and autoregressive reflection coefficients from it were used as features. In addition, the blink rate was evaluated via the electrical activity of the eyes to assess task performance (higher values indicate poorer performance). It is well-known that the performance of repetitive, boring or prolonged tasks often leads to lapses in vigilance, so the task was to detect such episodes. The author used a 3-min recording of wakefulness

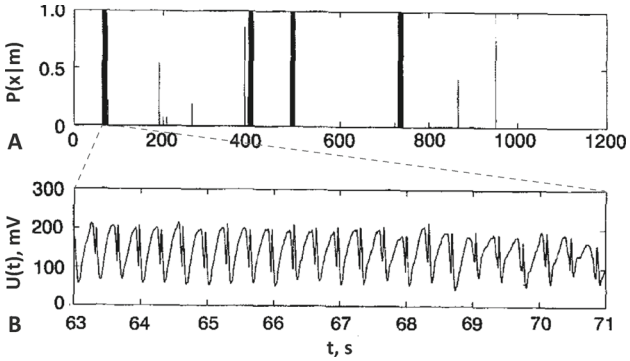

Fig. 4 **A** Novelty probability for epileptic seizure activity using EVT. **B** Time series for an episode flagged as novel. Based on materials from Roberts [60]

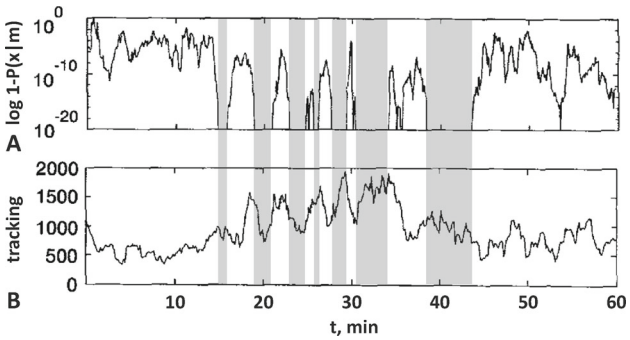

Fig. 5 **A** Novelty trace $log(1 - P(x|m))$ on *log* scale for vigilance data. **B** Tracking performance measure. Grey rectangles mark episodes of low novelty trace. Based on materials from Roberts [60]

and alertness as "normal" data, against which all subsequent data were screened for novelty. The results of the analysis are shown in Fig. 5. The plot on Fig. 5A shows $\log(1 - P(x|m))$ and is truncated at 10^{-20} for clarity. According to the author, several low episodes on the novelty trace (shown as grey rectangles on Fig. 5) correspond to the lapses in vigilance, since the subject's performance was also at its worst (see the high values on Fig. 5B).

Third, the author considered two more unconventional examples. They applied the technique to an anaesthesia data set consisting of a single channel EEG recorded during anaesthesia. The task was to assess the depth of anaesthesia, which is rather difficult due to the variety of anaesthetics and their effect on the EEG. The authors considered building a model of non-anaesthetised EEG activity and monitoring deviations from this in the unseen data. Data from seven non-anaesthetised subjects were used to model awake EEG. The unseen data, in which a subject was taken from the awake to the anaesthetised state, were then fed into the awake EEG model and the resultant EVT probability was able to detect the transition from one state to another. Figure 6 A shows the time course of $1 - P(x|m)$ for the data, and the transition from wake to anaesthetised state is evident.

In addition, the author implemented the approach to analyse magnetic resonance imaging (MRI) data. They used data consisting of a $100 * 100$ region of a slice through a tumour in the patient's brain. The author fitted the entire dataset with the GMM and then screened for novelty. As can be seen in Fig. 6B, there is a white region of very high novelty corresponding to the tumour location.

There is also an extension to the novelty detection approach based on multivariate extreme value statistics. This approach is based on multivariate extrema, which are maxima or minima in one or more dimensions in multidimensional data [63]. This also brings up an interesting topic: extreme events that exist in multimodal data. Clifton et al. [64] applied this method to a problem of vital signs monitoring. According to the authors, the main problem in this task is an unacceptably high number of false positives resulting from the analysis of a single vital sign channel. It is known that there are correlations between vital sign channels [65], and the authors tried to take advantage of this with multivariate EVT (mEVT). They tested the approach on data with two vital sign channels: heart rate (HR) and breathing rate (BR). The dataset included 332 high-risk adult patients with over 32,000 h of recordings and cardio-respiratory "crisis events" labelled. The authors used patients without crises as a training group and fitted their data with a bivariate Gaussian distribution. The novelty was tested against this distribution for all patients, including a test group with crises. The authors demonstrated that the mEVT-based approach yielded the same true positive detection rate but significantly fewer false positives than existing GMM-based approaches.

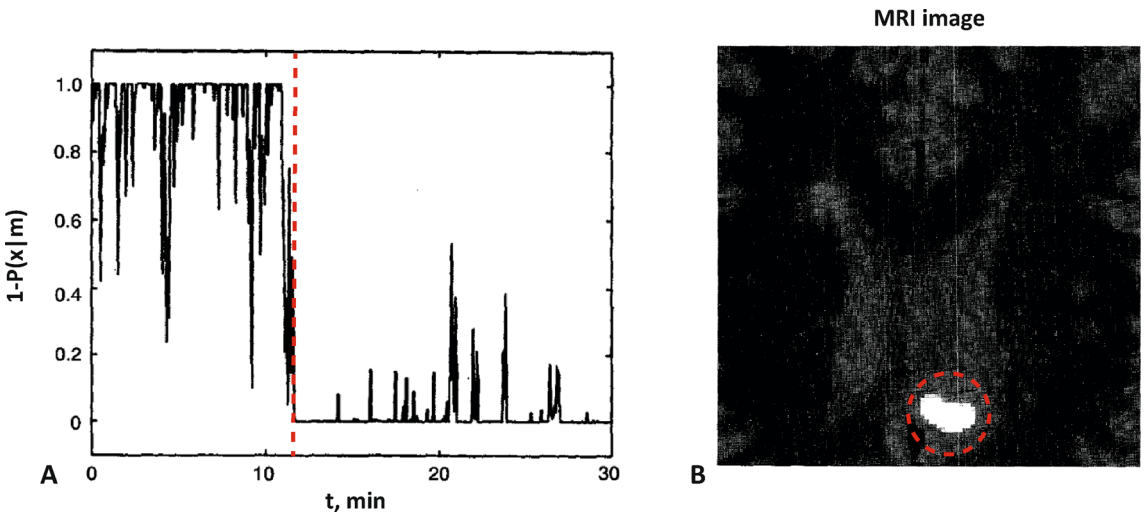

Fig. 6 **A** Novelty trace $1 - P(x|m)$ for anaesthesia data. The red dashed line marks the transition from the awake to the anaesthetised state. **B** Novelty probability superimposed on the MRI image. The red dashed circle marks the region of high novelty. Based on materials from Roberts [60]

5 Epileptic seizures as extreme events

As we discussed earlier, extreme events in biomedical data can be quite diverse, but the most striking examples are found in neurophysiological brain activity. This explains the bias in EVT-based publications towards studies of neural oscillations. This can also be seen in this brief review. Indeed, the rapid development of migraine attacks and epileptic seizures, which involve the sudden synchronisation of billions of neurons, exhibit dynamics similar to extreme events. It is also important that these dynamics have some properties of on–off intermittency [66–68]. According to Ansmann et al. [69], such self-induced switches between patterns in the dynamics are related to fundamental principles of extreme event generation in a "small-world" network, and these principles can be extended to natural systems such as the brain and the heart. In this context, it is possible to describe the mechanisms governing the generation of extreme events in the neural network of the brain by considering neuron-based mathematical models.

The concept of epileptic seizures as extreme events has been known for some time [70]. However, whilst in many fields of study, extreme dynamics have been effectively revealed and thoroughly described through time series analysis, research into epileptic extreme events has not been as thorough. Epilepsy is a common and dangerous neurological disorder [71]. Epileptic seizures vary from brief and almost undetectable episodes to long periods of violent convulsions, often accompanied by involuntary movements and a corresponding state of incapacity [72]. Patients with epilepsy can, therefore, create a potentially dangerous situation for themselves and others around them, and are often more prone to cognitive and behavioural deficits [73]. Epilepsy has a profound impact on the lives of patients, so antiepileptic treatment is essential. Seizures are usually controlled with medications [74] or, in drug-resistant patients, with surgery of neurostimulation [75, 76]. Regardless of the treatment, however, diagnosis is crucial. In this context, the use of EVT, together with traditional methods of spectral EEG analysis or more advanced machine learning approaches, could benefit the rapidly developing fields of early diagnostics and seizure prediction [77, 78].

In the recent years, there were several important papers in this area of research.

Pisarchik et al. [79] observed and analysed a specific type of extreme events occurring in the mouse brain after induced ischaemic stroke, i.e. post-stroke seizures. Animal models are often used in epilepsy studies to perform certain techniques that are not available in humans—for example, invasive EEG (electrocorticogram, ECoG) or other surgical procedures, such as those used to induce ischaemic stroke. Ischaemic stroke is known to trigger spontaneous neuronal activation resulting in the formation of synchronous EEG patterns. Such patterns are mainly associated with the development of another pathological brain activity—an epileptic seizure. This is known as post-stroke epilepsy and has been observed in both animal models and humans [80]. In their paper, the authors looked at the time–frequency structure of EEG signals associated with extreme events. For EEG analysis, they used continuous wavelet transform (CWT) with Morlet mother wavelet [81]. As the main CWT-based feature, they considered the wavelet energy W in the frequency range $f \in [1, 30]$ Hz and normalised it to the maximum energy in this range. To study extreme behaviour, the authors applied approaches from EVT: They constructed PDFs of

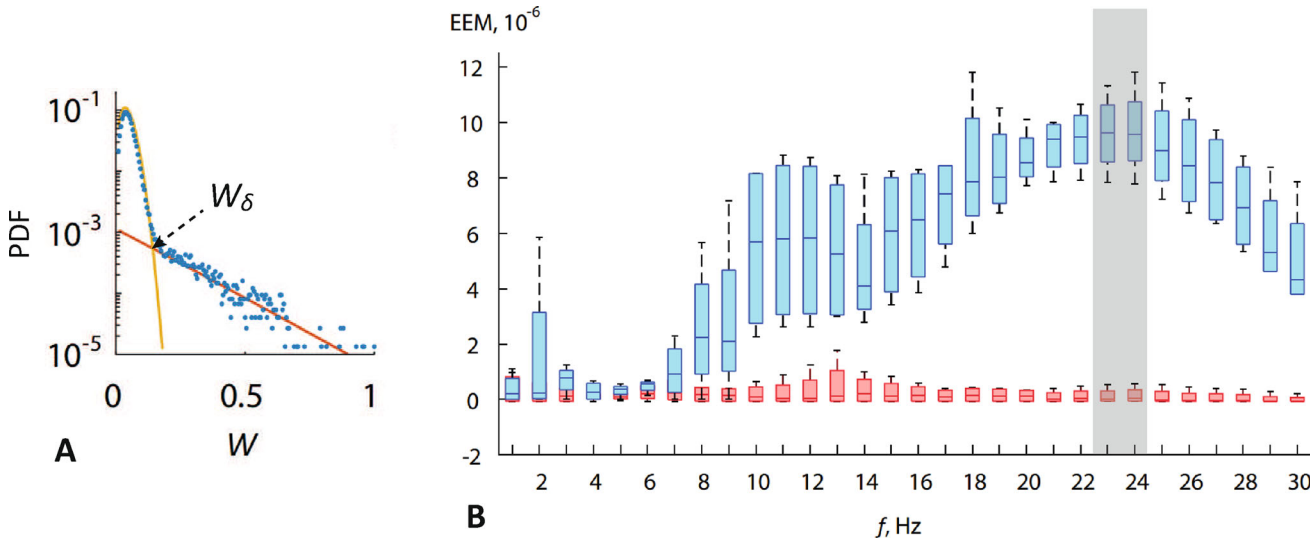

Fig. 7 **A** Distribution of wavelet energy amplitudes for the frequency band ∼ 20 Hz. Blue dots correspond to the empirical PDF $F(W)$, yellow curve is the Weibull distribution that fits the non-extreme part of $F(W)$, and red line is the GPD fitting the extreme part. The threshold W_δ between them is indicated by an arrow. **B** Box-and-whisker plot of EEM versus frequency for 6 healthy mice (coloured in red) and 6 mice with stroke (coloured in blue). The grey rectangle marks the frequency band with the most extreme brain behaviour. Based on materials from Pisarchik et al. [79]

wavelet energy at a given frequency and fitted them to certain theoretical distributions. The PDF of normal, non-seizure activity was perfectly fitted by the Weibull distribution, whilst the PDF for seizures was modelled by the GPD [37]. This result is illustrated in Fig. 7A. The authors conclude that this is consistent with the fundamentals of EVT, namely the Pickands–Balkema–de Haan theorem [36], as PDF shows a "heavy tail" in the presence of extreme events. Interestingly, this was only true for a narrow frequency band $f \in [22, 24]$ Hz associated with the occurrence of extreme events. Thus, the authors concluded that extreme events show a sharp, sudden increase in wavelet energy in a spectral range, whilst the energy at other frequencies remained almost unchanged. With this result in mind, the authors were able to develop a novel method for detecting and quantifying extreme events in the EEG. This method introduced the Extreme Event Measure (EEM), which aims to assess the heaviness of the PDF tail in EEG data by comparing it to the Weibull distribution. Using this technique, the authors demonstrated a difference between healthy and stroke mice, suggesting that the proposed method can be used for epileptic seizure detection, diagnostics, and prediction of central nervous system abnormalities. Figure 7B shows the comparison in EEM between healthy and stroke mice with the mentioned frequency band of the most pronounced extreme brain behaviour.

Frolov et al. [82] continued research in this direction using EVT to study the statistical properties of EEG recordings from six WAG/Rij rats with a genetic predisposition to absence epilepsy. WAG/Rij rats are an animal model for a particular form of epilepsy, known as absence epilepsy, which is characterised by the occurrence of spontaneous seizures in the form of spike-wave discharges (SWDs) in cortical and thalamic EEG [83]. Like Pisarchik et al. [79], the authors used CWT for time–frequency analysis of the EEG and calculated the normalised wavelet energy W_n. The subsequent analysis was similar: PDFs were constructed for normal state EEG and epileptic seizures, but in this case, both PDFs were fitted by the Weibull distribution with different parameters. An illustration of such a fit is shown in Fig. 8A. Once again, the analysis revealed an elongated tail of the epileptic PDF, which was related to the presence of extreme events according to the Pickands–Balkema–de Haan theorem [36]. The effect was found in certain frequency bands: $f \in [6, 9]$ Hz and $f \in [12, 18]$ Hz, which correspond to the main frequency of the SWD and its second harmonic (see Fig. 8B). These findings support the previous claim by Pisarchik et al. [79] that epileptic seizures manifest as extreme events in certain frequency ranges of the EEG.

The authors also considered the predictability of epileptic seizures. They considered time intervals between SWDs (return times) and showed that PDFs for them are fitted by a power-law distribution with power $-3/2$. This suggests the presence of long-range correlations and is in good agreement with previous studies of intermittent behaviour in the epileptic brain [67, 68, 84]. To prove the effect of data correlation observed in the PDF of return times, the authors used detrended fluctuation analysis (DFA) [85] to examine the wavelet energy at different frequencies. They showed that the DFA exponent is > 0.9 for 7 Hz and 14 Hz oscillations, suggesting a highly structural and self-organised behaviour. Based on the results obtained, the authors theorised that epileptic seizures can be predicted. To prove this, they considered several time intervals in the transition from normal EEG to epileptic seizures. The authors showed that the PDF of the wavelet energy at 7 Hz changes shape as it approaches

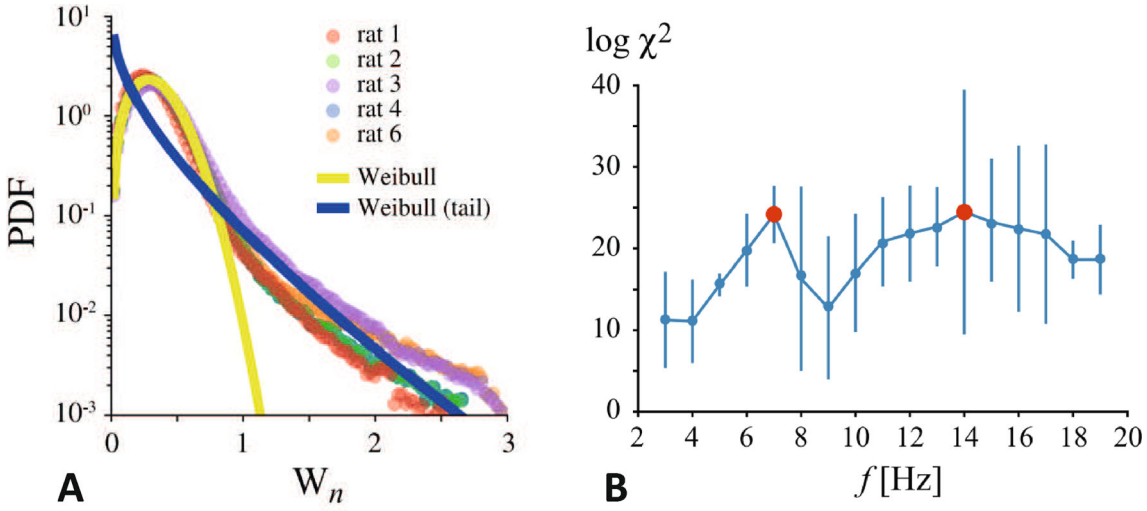

Fig. 8 **A** Distribution of wavelet energy amplitudes for the ∼ 20 Hz frequency band. Semi-log PDF plots of wavelet energy amplitudes during epileptic seizures. Coloured circles correspond to experimental PDFs obtained from the data of all five WAG/Rij rats. Curves are Weibull PDFs well-fitted to normal activity (yellow) and heavy tail (dark blue). **B** Semi-log dependence of Pearson's Chi-squared statistic χ^2 on oscillation frequency. Here χ^2 quantifies the difference between normal and pathological PDFs. Red dots indicate spectral components with maximum χ^2 values, and thus the highest degree of extreme behaviour. Based on materials from Frolov et al. [82]

the onset of the seizure. PDFs at different intervals were fitted by the Weibull distribution with different parameters, and monitoring changes in these parameters made it possible to predict epileptic seizures 1–7 s before onset. Examples of such PDFs and fitted Weibull distributions are shown in Fig. 9. The authors concluded that the presented results open a new possibility for early prediction of SWD from EEG signals.

Karpov et al. [86] extended the previously established concept to human subjects. The authors looked at long-term EEG recordings from patients with focal epilepsy. They calculated wavelet energy (power) in two frequency ranges: 1–5 Hz and 5–10 Hz, and showed that the lower frequency range corresponds to epileptic seizures in human patients. For reference, see the wavelet spectra for normal and epileptic activity in Fig. 10A. The wavelet energy averaged over this range was used to construct PDFs in baseline and seizure. Like Frolov et al. [82], the authors fitted these PDFs with Weibull distributions, and showed that certain parameters of the Weibull distribution were significantly different between baseline and seizure. However, only the Weibull for seizures has a heavy tail, and thus shows signs of extreme behaviour. See Fig. 10B, C for details. This result shows that epileptic seizures in humans can also be considered as extreme events in certain frequency ranges of the EEG.

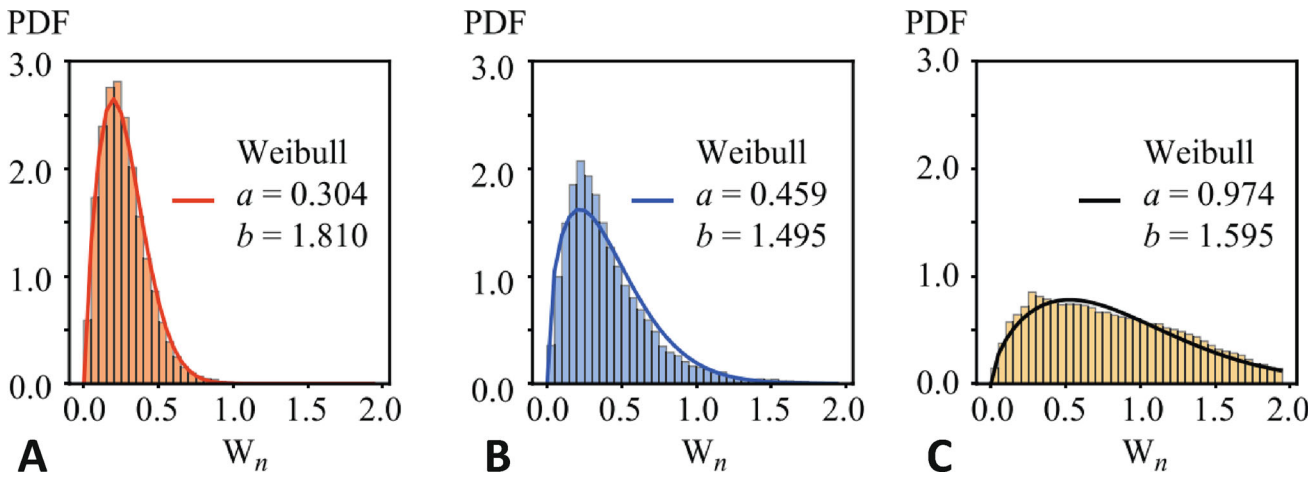

Fig. 9 PDFs of wavelet energy at 7 Hz (histograms) and fitted Weibull distributions (curves) with parameters a and b for different segments of the EEG close to seizure onset: far from the onset (**A**), before the onset (**B**), during the seizure (**C**). Based on materials from Frolov et al. [82]

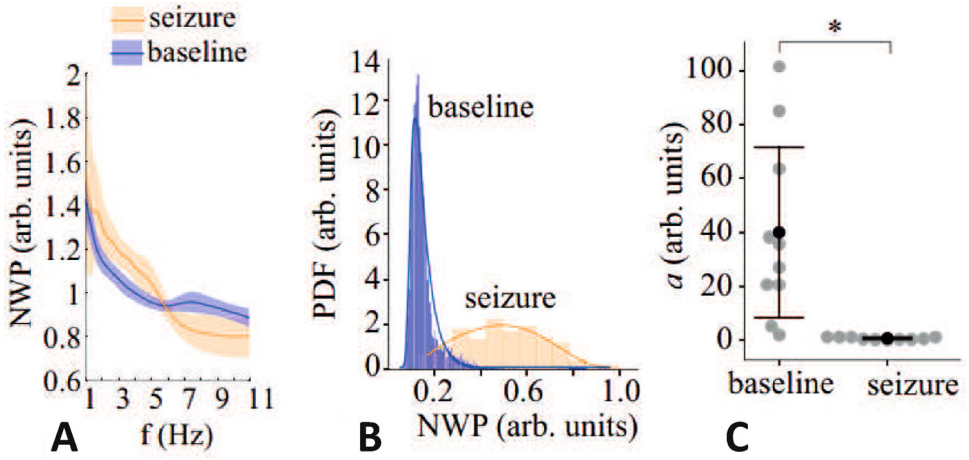

Fig. 10 **A** Wavelet energy corresponding to the epileptic seizure and the baseline. Data are presented as group means ± standard error. **B** PDFs of the local maxima of wavelet energy in the 1–5 Hz frequency band (histograms) and their Weibull fits (curves) for the epileptic seizure and baseline. Data are presented for a single subject. **C** Pairwise difference distribution for the Weibull exponentiation parameter a. Based on materials from Karpov et al. [86]

In addition, the authors theorised about possible mechanisms for the onset of epileptic extreme events. They considered the results of Frolov et al. [82] and suggested that extreme events occur due to instability, and that the brain, like many other dynamical systems, may exhibit prebifurcation noise amplification near a critical point prior to the onset of a seizure. To test this hypothesis, the authors estimated noise intensity and signal variance in several time windows. They considered four time intervals, T_1, T_2, T_3, T_4, gradually approaching the onset of the seizure. The length of each interval was 30 s with 50% overlap between intervals, the first interval (T_1) starting 75 s before onset. For details, see Fig. 11A. The results of the ANOVA test showed that both noise intensity and

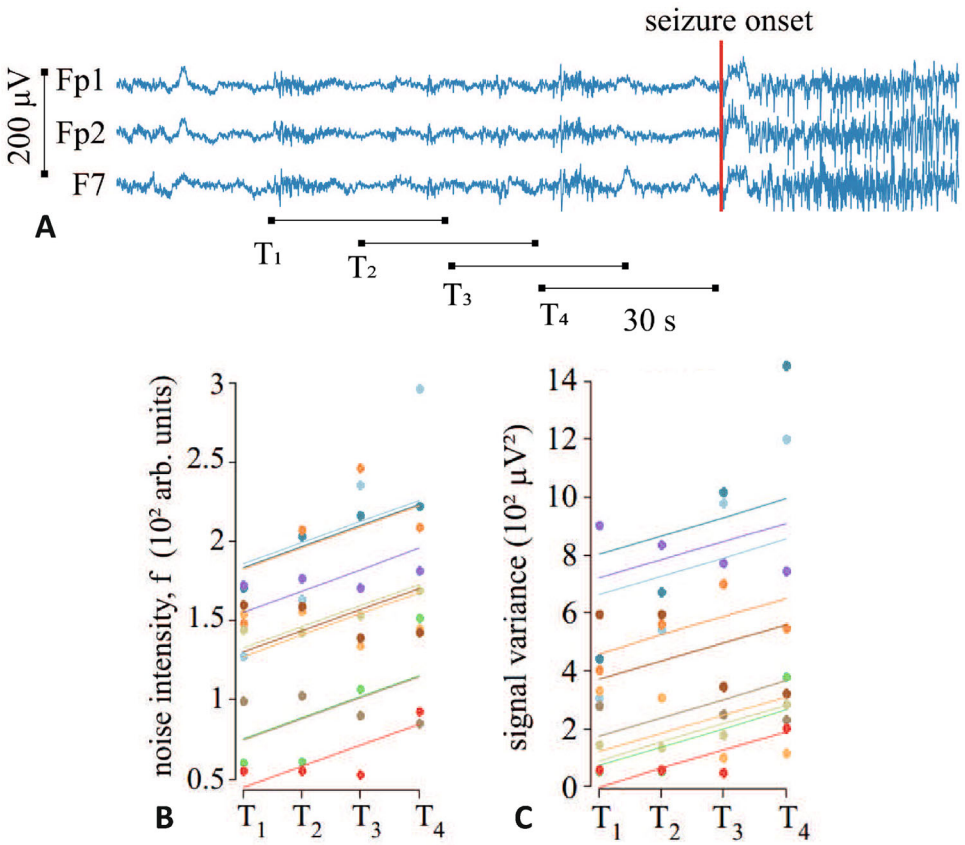

Fig. 11 **A** EEG data with seizure onset and four time intervals T_1, T_2, T_3, T_4 that gradually approach the onset. Regression plots for noise intensity (**B**) and signal variance (**C**) in four time intervals T_1, T_2, T_3, T_4. Different colours correspond to data from different subjects. The lines have a similar slope: $r = 0.52$ for noise intensity and $r = 0.38$ for signal variance. Based on materials from Karpov et al. [86]

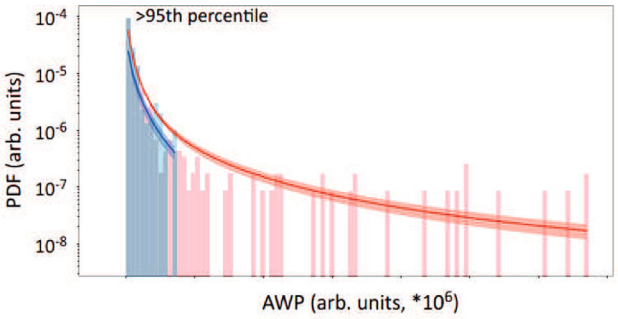

Fig. 12 PDFs of averaged wavelet energy (histograms) and fitted Weibulls (curves) for two groups of participants: with recall close to 1 (red) and recall close to 0 (blue). Based on materials from Karpov et al. [49]

signal variance gradually increased as seizure onset approached. These results are shown in Fig. 11B, C. Thus, the authors concluded that this behaviour may be part of the onset mechanisms of epileptic extreme events shared between rats and humans.

In the follow-up paper by Karpov et al. [49], the authors discussed how EVT can help in seizure detection. They considered EEG wavelet energy averaged over the seizure frequency band (2–5 Hz), the typical seizure time interval (60 s), and all EEG channels (25). The authors showed that the PDF for this averaged energy was fitted by a Weibull with a heavy tail, showing signs of extreme behaviour. They speculated that epileptic extreme events were outliers and used this reasoning to implement outlier detection techniques in seizure detection. The authors used a one-class support vector machine (SVM) approach with features based on averaged wavelet energy. These features and the chosen algorithm were based on expert level domain knowledge of epileptic activity in the EEG; thus, the authors underlined the explainability of this approach. They also emphasised that this is an unsupervised machine learning method, so it does not rely on labelling data and training classifiers in advance. The authors proved their point by testing the proposed method on raw clinic EEG data, achieving up to 77% recall and 13% precision. Given the decent recall and low precision, they theorised that this approach could be implemented in a Clinical Decision Support System (CDSS) that flags possible seizures and leaves the final decision to a human. This approach could reduce the workload of medical experts who manually mark seizures. The authors also pointed out that the SVM performed poorly for some patients, and the PDFs of the wavelet energy for these patients lacked signs of extreme behaviour. PDFs and fitted Weibulls for two groups of patients are shown in Fig. 12. It can be seen that only the PDF for the high recall group shows a heavy tail of extreme dynamics. The authors concluded that the presence of extreme behaviour is crucial for good performance of such outlier detection methods. This result is particularly interesting in the context of existing models of extreme behaviour [87, 88]. Later, Karpov et al. experimented with various supervised and unsupervised algorithms and features to improve the quality of seizure detection [89, 90].

The research by Luca et al. [91] is in line with the previously mentioned studies. Although the authors did not consider EEG signals, they applied EVT to analyse motor activity in children with epilepsy. 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. In some ways, this approach is very similar to that proposed by Karpov et al. [49]. This result is interesting because hypermotor activity during seizures is generally considered to be disruptive, whereas in Ref. [91], it was used for seizure detection. In the Introduction, we mentioned two types of outliers (parasitic and data inherent) and discussed how the outliers of the first type should be removed, whilst the second type can provide information about the system. However, the results of Luca et al. suggest that these two types can be mixed and should, therefore, be analysed with care.

6 Conclusion

In this paper, we have provided a brief review of the study of extreme events in biomedical data. This included consideration of different types of extreme behaviour in living systems and their corresponding manifestations in different biomedical signals. We also explored concepts of EVT used in applied tasks as well as for understanding fundamental mechanisms of living systems.

The research discussed in Sect. 3 shows that the mere presence of extreme dynamics in biomedical data can provide insight into the state and evolution of the living system. The direct implementation of EVT, sometimes with additional steps, is often sufficient to detect and describe extreme behaviour. EVT is superior to most traditional methods that focus on mean behaviour. Extreme events occur in various types of biomedical data and are often associated with pathology, but can also mark the state of enhanced performance, for example in the brain. In

this way, EVT is a promising tool for analysing trajectories and potential risks for certain patients in the group, without having to delve deeper into the analysis of individual dynamics.

The works observed in Sect. 4 are dedicated to certain applied methods for extreme event detection. Novelty detection basically equates "novelty", "outliers" and "extreme events", so this approach should be considered with caution. In this context, both external noise and intrinsic extreme dynamics are considered "novelty". In addition, "novelty" sometimes arises from state changes that are not necessarily extreme in nature. Whilst novelty detection is often based on EVT, not every "novelty" is an extreme event, at least not in the sense described in this paper. Thus, under certain conditions and limitations, novelty detection can be used to detect individual extreme events in biomedical data.

Section 5 shows, using epilepsy studies as an example, that the application of EVT concepts in living systems research has recently received considerable attention, albeit in a limited area. The reviewed papers demonstrate that EVT can be used not only in purely applied areas of diagnostics and crisis prediction, but also to gain insight into fundamental mechanisms in living systems. Furthermore, these studies show that EVT can be successfully combined with other approaches such as spectral analysis and machine learning. We believe that future research on biomedical data could benefit from adopting this approach.

The topic of Sect. 5 is particularly promising, and its further development may include several directions. First, the authors could implement methods based on the cumulative distribution function (CDF) as opposed to the PDF, since CDF methods are known to be more stable for the numerical analyses. This could help to separate extreme behaviour from the norm, and thus introduce stricter criteria for detecting epileptic activity in the EEG. Second, the authors could delve deeper into the biophysical mechanisms responsible for the occurrence of epileptic extreme events. For example, the exciting topics of criticality and quasicriticality or multivariate extrema mentioned in this review should be investigated in the context of epilepsy.

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Data availability No data are associated.

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