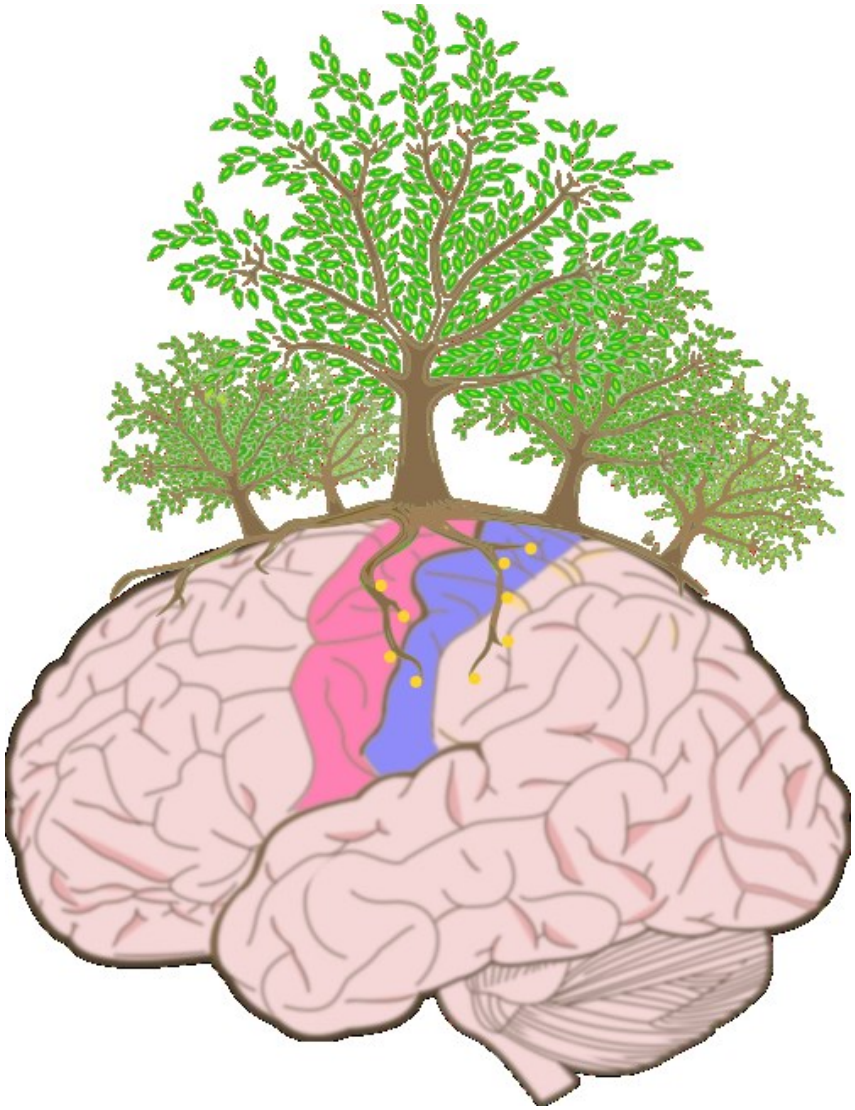
Online seizure onset detection for responsive stimulation in the sensorimotor cortex



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(Cover image: the sensorimotor path to a random forest)

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Summary

Background: Many patients with focal epilepsy arising from the pericentral gyri suffer from refractory seizures. When they present for epilepsy surgery, large parts of the pericentral gyri are considered surgically unamenable without causing permanent functional deficits, due to the region's key role in sensorimotor processing. Responsive cortical electrical stimulation (CES) may be a promising alternative to surgery. It is unclear how much of the reported effect of responsive CES is actually due to closed-loop seizure suppression and how well these seizures are recognized by intelligent systems. Improved approaches for highly specific and fast seizure detection, validated on central lobe epilepsy (CLE) patients, are required for the development of a new generation of intelligent implantable responsive CES devices. This study aims to employ a combination of existing machine learning methods, which have demonstrated sensitive and specific real-time classification of the ictal and non-ictal electrocorticogram (ECoG), and compare the performance of the combined algorithm with a reference algorithm similar to the algorithm used in an existing responsive CES device *(RNS Neuropace)*.

Methods: A systematic literature review was performed to establish which features and classifiers are likely to have a high sensitivity and low false detection rate (FDR) for detecting seizure onset in ECoG. Based on the literature review, a 138-dimensional feature space, consisting of cross-correlation features and a set of per-channel time and frequency domain features was chosen to be used in a patient-specific machine learning algorithm. Recordings of ten CLE patients, who had at least three seizures with similar onset characteristics during presurgical intracranial evaluation in the University Medical Center Utrecht, were used. Six bipolar ECoG channels were selected for each patient to represent cortical areas inside and outside the clinically identified seizure onset zone. Features were extracted from 1s epochs of ictal and interictal ECoG data. To explore the feature-space, a nonparametric test was performed to find sensitive features and rank the features by their class separability to explore the feature space. A Random Forest (RF) classifier was trained for each patient and early detection (<10s) sensitivity was obtained from seizure-level leave-one-out cross-validation. The FDR was determined using a 24h interictal test set from the same patient the classifier was trained on. As an approximation of the *Neuropace* detection scheme, a line-length based thresholding algorithm was used, for which same performance metrics were obtained.

Results and Conclusion: In the literature, relatively simple classifiers such as RF outperform more complex classifiers and they have been shown suitable for low-power applications. Based on patient-specific separability rankings, the most promising feature types in the used set are line-length, gamma power, beta power, power ratio, fluctuation index, variance, time-series cross-correlation, frequency cross-correlation, and eigenvalue of the frequency cross correlation. The algorithm, consisting of the full feature space and RF classifier, demonstrates an improvement of early detection sensitivity (98% mean) and FDR (1.53/h mean) as compared to the reference algorithm, while maintaining a short detection delay (3.9s mean). The used feature set and patient-specific RF classifier may be employed to achieve closed-loop seizure suppression in future responsive CES implants for CLE treatment.

Contents

List of abbreviations

AED	antiepileptic drugs
AUC	area under the curve
BIDS	Brain Imaging Data Structure
BLDA	Bayesian linear discriminant analysis
CART	classification and regression tree
CES	cortical electrical stimulation
CLE	central lobe epilepsy
DFT	discrete Fourier transform
DWT	discrete wavelet transform
ECoG	electrocorticogram/electrocortigraphy
EEG	electroencephalography
FDR	false detection rate
FI	fluctuation index
GMM	Gaussian miture models
iEEG	intracranial electroencephalography
ILAE	International League Against Epilepsy
MAD	mean absolute deviation
NSO	not (involved in) seizure onset
PSD	power spectral densities
REC2Stim	Rational Extra-eloquent Closed-loop Cortical Stimulation
RF	random forest
RNS	responsive neurostimulation (*Neuropace*)
ROC	receiver operating characteristic
sEEG	stereo electroencephalography
SO	(involved in) seizure onset
SR-EMD	sparse representation-based earth mover's distance
STFT	short time Fourier transform
SVM	support vector machine

1. Introduction

Epilepsy is a common neurological disease, with a prevalence ranging from 0.3% to 1.2%[1]. It is characterised by recurrent episodes of dysfunctional brain activity associated with changes in behaviour. These episodes are called seizures, defined as "a transient occurrence of signs and/or symptoms due to an abnormal excessive or synchronous neuronal activity in the brain"[2]. The clinical manifestations of seizures vary greatly, including loss of awareness and disturbances of movement and sensation[3].

Despite the high number of antiepileptic drugs (AED) available, approximately one third of treated epilepsy patients remain suffering from seizures and are classified as refractory to medical management after two failed AED trials[4]. For these intractable patients, other treatments are considered, such as ketogenic diet or, in case of focal epilepsy, resective surgery and laser ablation of the epileptogenic tissue[5]. Before any attempt at removing cortical tissue is made, the epileptogenic zone[6] and the eloquent cortex are mapped to plan such a surgical intervention. This pre-surgical evaluation includes seizure semiology, magnetic resonance imaging and electroencephalography (EEG) and sometimes functional magnetic resonance imaging, magnetoencephalography, ictal single-photon emission computed tomography, and intracranial EEG (iEEG) monitoring. The evaluation may indicate an epileptogenic zone overlapping with or adjacent to eloquent cortex[7], such as the primary sensorimotor cortex.

The pericentral sensorimotor cortex and its surroundings are a common location for focal cortical dysplasia, often leading to intractable epilepsy characterised by hemiclonic or tonic-clonic seizures. Localisation of the seizure focus in this cortical area is facilitated by the somatosensory symptoms usually presented in a confined body part, corresponding to a contralateral representation in the somatotopically organised central area of the cortex, and spreading semiology according to the somatotopic arrangement along the central sulcus (Jacksonian march[8]). Because the central gyri play a key role in sensorimotor processing, large parts are considered to be inoperable without permanent functional deficits, especially regarding fine intended movement and motor learning.[9]

Electrical stimulation has been used as an alternative method to manage inoperable epilepsies, through cortical electrical stimulation (CES) directly on the epileptogenic zone or highly connected cortical areas. Short-term continuous CES has shown to be capable of reducing seizure rate[10]. Both open-loop and closed-loop CES approaches have been used[11]. Open-loop approaches use pre-scheduled or chronic stimulation, whereas closed-loop approaches only stimulate in response to signals of an impending or starting seizure. Closed-loop CES requires continuous brain activity monitoring using intracranial electrodes and early automated seizure onset detection to allow for responsive stimulation, in order to prevent or terminate clinical symptoms of seizures.

The RNS System by *Neuropace* is currently the only approved implantable responsive neuro-stimulator for cortical stimulation as a treatment for epilepsy[12]. Although this device has proven efficacy both under short-term and long-term application[13], it suffers from a high number of false detections (estimated to be 25 to 83 false detections per hour[14]). This complicates the assessment of the effectiveness of closed-loop suppression of seizure-related ictal activity. Improved approaches of seizure detection with higher specificity are thus required.

Online electrographic seizure detection

Due to high variation of the EEG patterns that characterize a seizure[15], the variability of background EEG activity among patients, as well as intra-individual fluctuations in EEG activity, the challenge of automated seizure detection in the EEG has been an active field of research for over three and a half decades[16]. Early seizure detection poses a difficult problem as seizure onset patterns are diverse and may closely resemble interictal epileptiform bursts that can occur frequently between seizures[17].

Electrographically, seizure onset may be characterised by onset patterns such as low voltage fast activity, rhythmic sharp waves, repetitive spiking, rhythmic alpha waves, rhythmic beta waves, rhythmic theta waves or amplitude depression[18]. Multiple onset patterns may even occur in the same patient. Little research has been done to characterise epileptic activity in the pericentral gyri of the brain cortex specifically. The primary motor cortex is known to microscopically differ from other neocortical areas, in that it contains strongly developed infra-granular layers[19]. In the EEG, the sensorimotor areas present mu-rhythms when the body is at rest. These properties may have an impact on automated seizure onset detection in this specific cortical area.

Several signal properties at seizure onset have been identified that can be used for seizure onset detection in iEEG, or more specifically electrocortigraphy (ECoG) signals[15]. Fast activity was noted to be a common pattern being observed across different pathologies, including mesial temporal atrophy and focal cortical dysplasia[18]. Additionally, ripples (>80Hz) are observed in many seizure-onset patterns[6,20]. Oscillations in beta-gamma-ripple bands have previously been used to identify seizure onsets in the University Medical Center Utrecht epilepsy monitoring unit for the development of a seizure alarm[21]. The used threshold algorithm showed a false detection rate (FDR) as high as 1/h on a subset of patients. The algorithm was not sensitive to the seizures of three patients suffering from sensorimotor epilepsy[22], which makes the algorithm unsuitable for general use in closed-loop CES targeting the primary sensorimotor cortex.

Features and algorithms

For many other existing seizure detection algorithms, methods from the field of machine learning have been employed to classify the ictal ECoG and non-ictal ECoG in real time[23]. These seizure detection algorithms consist of a feature extraction part and a classification part. In the feature extraction part, raw or pre-processed ECoG data is analysed in various ways in order to extract relevant features to pass to the classifier. In the classification part, feature values or subsets thereof are analysed and classified as being indicative of a seizure pattern or not. Detecting seizure onset patterns in the sensorimotor cortex requires comprehensive and discriminative features, to be extracted from the ECoG signal. Both linear and nonlinear features have been employed in existing detection algorithms.

Due to their simplicity and versatility, several linear features have been employed in the area of seizure detection. Examples are the variance of a signal, which represents the dynamics in the underlying ECoG, and features based on autocorrelation, exploiting the periodic nature of seizures. Alternatively, the spectral characteristics of a signal can be estimated using e.g. linear prediction filters, Fourier transform, or wavelet transform, which all can be used to detect changes in the spectral density at seizure onset. Other linear features include the (relative) fluctuation index, which relies on the assumption that there is an increased intensity of fluctuation in the ECoG signal during a seizure[24].

Nonlinear analysis of ECoG has received increasing interest as it incorporates the non-stationary nature of the ECoG signal. For example, many estimation algorithms have been developed for the fractal dimension, which characterises the complexity of a time series[25]. Alternatively, a metric for

the exponential divergence of time series trajectories in the phase space, called Lyapunov exponent, characterises the ECoG's chaotic nature has been used[26]. Other nonlinear measures include information theory based entropies, which describe the irregularity, complexity or unpredictability of a signal[27].

A challenge in the field of seizure detection is the lack of reproducible validated algorithms. While many seizure detection algorithms have been published[28,29], few studies have been carried out to assess the reproducibility of algorithm performance. Thus, these algorithms likely suffer from overfitting of the dataset used for development. Whereas reviews of features for seizure detection are available[30], and the selection of features for online seizure detection in scalp EEG has been thoroughly addressed by Logesparan *et al.*[28], there is no exhaustive overview of promising features applicable to intracranial recordings, let alone to online ECoG on the sensorimotor cortex specifically.

Aims of the study

In this study, we develop an algorithm that can detect different seizure onset patterns in the ECoG, relevant for implementation in closed-loop CES on the sensorimotor cortex. We employ methods from other studies that have demonstrated a highly sensitive and specific classification of ictal and non-ictal iEEG in real-time. The steps of the project are threefold:

- Chapter 2: A systematic literature review is performed to establish which algorithms are likely to have a high sensitivity and low FDR for detecting seizure onset in ECoG.
- Chapter 3: Based on the literature review, features from the most promising algorithms for the purpose of detecting seizure onset in ECoG are combined to build a detection algorithm that can be implemented in closed-loop CES. The characteristics of the selected features are evaluated on clinical data.
- Chapter 4: The features are used with a classifier and the algorithm is validated in a retrospective study using ECoG data from the University Medical Center Utrecht epilepsy monitoring unit. The performance is compared with a seizure detection algorithm similar to the algorithm used in the *Neuropace* responsive neurostimulator.

2. Literature review

The literature review aims at comparing existing seizure detection algorithms for ECoG data. To possibly achieve true closed-loop suppression in responsive CES implants, highly specific and fast seizure detection approaches are required. This review sought to establish which algorithms may have a high sensitivity and low FDR in detecting seizure onset. The following review questions were addressed:

- Which features extracted from the ECoG data are most likely to distinguish between seizure onset and background activity, i.e. by showcasing the best sensitivity and FDR, in a convincing sample (i.e. benchmarking set or at least >10 patients, >80 seizures, >100 hours)?
- Which classifiers are used to classify the ECoG signal?

2.1 Methods

Inclusion criteria

1. Seizure detection/prediction algorithm was designed especially for ECoG data (i.e. iEEG using cortical electrodes, e.g. grid or strip).
2. Involving an algorithm that is able to automatically detect seizure onset
3. Either on-line early detection or short-term (<1min) prediction was the aim of the algorithm
4. Studies that verified the used algorithm in (human) clinical data
5. Publication 2009-2018
6. Language of publication: English

Exclusion criteria

1. Exclude delineation-, mapping-, localization-only studies
2. Exclude exclusive depth electrode based detection (i.e. stereo EEG; sEEG)
3. Exclude exclusive scalp EEG, thalamic or hippocampal based detection
4. Exclude high-density grid based detection
5. Exclude focus on high-frequency oscillations
6. Exclude non-human only experiments

Articles were chosen based on the inclusion and exclusion criteria. Additional articles were chosen from the reference lists of already included publications if they were published since 2009. In addition to the mentioned inclusion and exclusion criteria, all articles aiming at the prediction of seizures more than 1 minute before the seizure onset were excluded.

The used validation methodology and the obtained performance results were analysed. Articles that validated an existing algorithm on a broader dataset, selected validation subjects to represent different seizure onset patterns, or showcased the best performance using a complete benchmarking set were further evaluated.

Search strategy

In PubMed:
(electrocorticogra*[Title/Abstract] OR ECoG[Title/Abstract] OR “intracranial EEG”[Title/Abstract] OR iEEG[Title/Abstract] OR intracranial electroencephalograph*[Title/Abstract])
AND
(automat*[Title] OR predict*[Title] OR detector[Title] OR detection[Title])
AND
(seizure[Title] OR ictal[Title] OR epilep*[Title])
NOT
(delineat*[Title] OR map*[Title] OR localiz*[Title] OR outcome[Title])
AND
("2009"[Date - Publication] : "3000"[Date - Publication])

2.2 Results

The search in PubMed resulted in 140 articles. After reading titles and abstracts, 56 articles remained which seemed to meet all initial inclusion criteria. After closer inspection of the methodology, subjects and performance indicators used, and after reducing the set of articles by excluding the articles aiming to predict seizures more than 1 minute before onset, 27 articles remained for review (**Figure 1**).

These studies varied greatly in their detection algorithms, as well as the subjects used for validation. Performance indicators of interest were either a combination of sensitivity of seizure events, detection delay, and FDR per hour, or a standardised area under the curve (AUC) for early (<10 s) detection. To establish whether the algorithms are properly validated, the validation methodologies were first analysed before proceeding to evaluation of the used features.

Datasets used for validation

In the reviewed literature, a variety of datasets was used to validate the algorithms. A recurring (13 articles) benchmarking set of subjects is the *University of Freiburg*'s data pool[31,32] comprising of over 600 hours of iEEG data and 88 seizures from 21 patients. Later studies (4 articles) made a selection of subjects from the successor of the *Freiburg* dataset, the *European Epilepsy Database*[33]. Several publications (4 articles) used the dataset from the *University of Pennsylvania* and *Mayo Clinic*'s Seizure Detection Challenge[34], consisting of iEEG recordings obtained from 4 dogs with naturally occurring epilepsy and 8 patients with temporal and extra-temporal lobe epilepsy. One paper used data from the *iEEG portal*[35]; others from their own respective Epilepsy centres (3 articles), or had not specified the origin of the used clinical iEEG data (3 articles). No study validated exclusively on patients with focal epilepsy in the sensorimotor cortex.

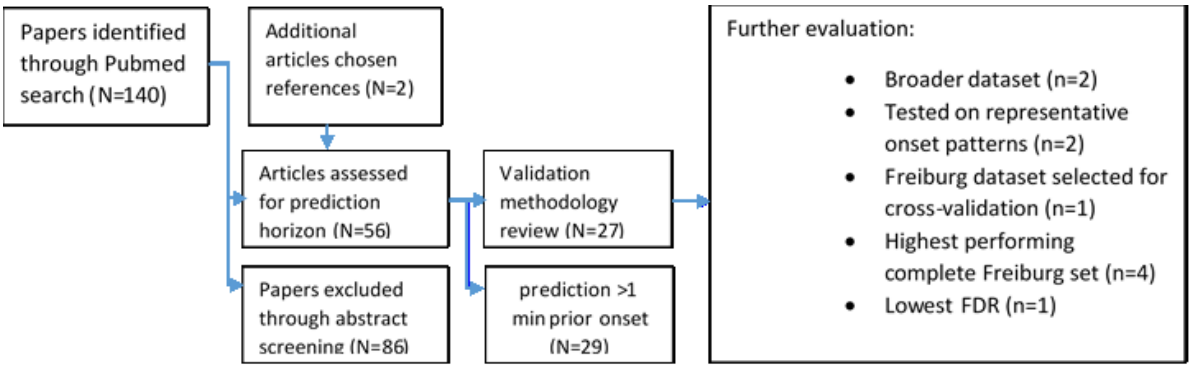


Figure 1| Review flow chart

Further evaluation of used features and classifiers

The features from two studies that validated an algorithm on a broader dataset[36,37], and two studies that selected subjects to represent different seizure onset patterns[14,38], were further evaluated. Additionally, from the studies that used the *Freiburg* dataset, the features of the study that applied cross validation with three seizures per subject[39], as well as those that included all subjects and had an outstanding performance (i.e. sensitivity > 93% average FDR < 0.25/h) in their validation were further evaluated. Other studies that used a small sample (n<10) of patients without accounting for the selection of these patients were not further evaluated. In total, further evaluation was performed for features of 10 studies, representing 12 algorithms (**Table 1**).

Table 1 | Overview of analysed studies and algorithms

Entire separate algorithms in the same study are shown in their own row (2-4). Some studies employed multiple classifiers on the same feature space. RF: Random Forrest, SVM: Support Vector Machine, NN=Neural Network, CART: Classification and Regression Tree, AdaBoost: Adaptive Boosting, BLDA: Bayesian Linear Discriminant Analysis, GBoost: Gradient Boosted, DT Decision Trees, LR: Logistic regression. AUC (<10s): Area under the curve for early seizure detection (within 10 seconds from seizure onset), FDR: False detection rate, DWT: Discrete wavelet transform, GMM: Gaussian mixture models, SR-EMD: sparse representation-based Earth Mover's Distance. MAD: Mean absolute deviation.

Study (algorithm)	Time-domain features	(Time-)Frequency-domain features	Classifier	Performance
Manzouri *et al.* [38]	Mean MAD Variance Skewness Kurtosis Line length Autocorrelation	Average power in beta (13-30Hz) Average power in gamma (30-50Hz) Power ratio between alpha, beta and gamma bands	RF SVM	AUC (<10s): 0.90 (RF) 0.83 (SVM)
Baldassano *et al.* [37] **(Hills)**	Pairwise cross-correlation Sorted cross-correlation eigenvalues	Normalised frequency magnitudes 1-47 Hz Pairwise cross-correlation Sorted cross-correlation eigenvalues	RF	AUC (<10s): 0.966
Baldassano *et al.* [37] **(Olson & Mingle)**	Covariance of 3 selected bandpass signals (5-200Hz)	-	NN	AUC (<10s): 0.925
Baldassano *et al.* [37] **(Talukdar, Moore & Sood)**	Maximum amplitude Mean amplitude Absolute deviation Variance *Global:* Maximum amplitude mean amplitude Maximum absolute deviation Maximum Mean Variance of the variance Covariance between channels	Maximum power Mean power Variance Maximum power frequency *Global:* Maximum power Mean power Maximum variance Maximum max frequency Mean max frequency Variance of max frequency	RF	AUC (<10s): 0.970
Zhang and Parhi[39]	-	(Prediction error filter signal based) Power Log sum 3 Wavelet decomposed powers 3 Wavelet decomposed log sums	SVM AdaBoost	Sens: 95.0% FDR: 0.12/h (SVM Sens: 98.8% FDR: 0.075/h (AdaBoost)
Zhang and Parhi[40]	-	Absolute spectral power in 13 subbands (3-400 Hz) Relative spectral powers Spectral power ratios	CART+SVM	AUC (<10s): 0.914
Yuan S *et al.* [41]	-	SR-EMD between GMM using three DWT bands (4–8 Hz, 8–16 Hz, 16–32Hz)	BLDA	Sens: 94.9% FDR: 0.223/h
Zhou *et al.* [42]	-	Lacunarity (from 3 DWT bands) Fluctuation index (from 3 DWT bands)	BLDA	Sens: 96.25% FDR: 0.13/h
Shoaran et al.[36]	Line length Variance	Power Power in Delta, Theta, Alpha Beta, Gamma, Ripple, Fast Ripple	GBoost DT	Sens: 98.3%
Donos *et al.* [14]	Mean MAD Variance Skewness Kurtosis Autocorrelation	Power in infra-slow (0.1-0.5Hz) Power in beta (13-30 Hz) Power in gamma (30-128 Hz) Power-ratio between alpha (7-13Hz), beta and gamma bands.	RF	Sens: 93.84% FDR: 0.33/h
Bandarabadi *et al.* [43]	-	(Bipolar) power ratio (12–26Hz and 0.5-3Hz)	Threshold	Sens: 86.9% FDR:0.06/h
Yan et al. [24]		*Stockwell transform:* Delta (0.4–4Hz), Theta (4–8Hz), alpha (8–12 Hz), beta (12–30 Hz) power in three sub-epochs	GBoost LR	Sens: 94.26% FDR: 0.66/h.

Feature sets

The simplest feature set included only power bands (delta-beta)[24]. It was designed to evaluate 4s-epochs, deriving the power band features from three sub-epochs. This epoch length causes a minimum delay of 4 seconds. Another simple feature set only uses a power ratio (12–26Hz divided by 0.5–3Hz) in bipolar channels[43]. Bipolar signal are considered to be a measure for neuronal potential similarity, as contains information of both amplitude similarity and phase synchrony between brain regions, which is typical for ictal activity.

Donos *et al.*[14] applied a simple seizure detection algorithm meant for closed-loop CES. In their system, eleven features from the time and frequency domains are computed for each monopolar (average re-referenced) iEEG channel, i.e. mean, mean absolute deviation (MAD), variance, skewness, kurtosis, autocorrelation, line length, power in infra-slow frequency band (0.1– 0.5Hz), beta (13–30Hz) and gamma (30–128Hz) bands and a power-ratio between the alpha (7–13Hz), beta and gamma bands. In their recent comparison of two classifiers, Manzouri *et al.*[38] used ten of these time and frequency domain features, selected based on a reasonable computational demand. They found that the complex calculations for autocorrelation had a relatively large impact on runtime. In feature importance studies by Shoaran et al.[36], line-length and a patient-specific single spectral power turned out to be dominant features in their algorithm.

Zhang and Parhi [39] extracted features using a two-level wavelet decomposition. Three disjoint sub-bands are decomposed and each total power is used as a feature, as well as the logarithm of the product of the absolute values of each. Later they used a feature reduction algorithm (CART) to automatically reduce the amount of spectral features to 3 or 4 features to achieve early seizure detection[40]. Non-linear approaches from the field of Brain Computer Interfaces were used in two feature sets, both based on three discrete wavelet transform (DWT) bands (4–8 Hz, 8–16 Hz, 16–32Hz)[41,42].

When using multiple channels, the use of global features may provide additional information to the classifier. Pairwise cross-correlations and sorted eigenvalues in both time- and frequency (1-47 Hz) domain, was shown to be quite effective to classify 1-s segments (early AUC 0.967)[37]. Other covariance or cross-correlation based algorithms confirmed the high performance when using these global features (early AUC 0.970)[37].

Choice of classifier

A Random Forest (RF) classifier, or other ensemble classifier was used by eight of the evaluated algorithms[14,24,36–39]. It is considered to be of particular interest for early seizure detection in closed-loop CES, because of its relative resistance to overtraining, ability to efficiently work with large data sets, no need for normalization of features, few required parameter optimizations and the evaluation of features' importance by measuring the mean decrease in the Gini index[44]. The Gini index is a measure of how often a randomly chosen element from the set would be incorrectly labelled, if it was randomly labelled in accordance with the distribution of labels in the subset. Overall high performances were achieved in diverse seizure onset patterns. With delay optimisation, a delay of 3s was achievable with 93.84% mean sensitivity and 0.33/h FDR[14].

In two studies.[42,45], Bayesian linear discriminant analysis (BLDA) was used to classify 4-s epochs from three channels and achieved sensitivity of 96.25% and a FDR of 0.13/h with a mean delay time of 13.8s. The system performed less well when using shorter epochs[41].

A Support Vector Machine (SVM) classifier was used by three of the evaluated algorithms[38–40]. In combination with a classification and regression tree for feature selection, Zhang and Parhi achieved high performance (early AUC 0.914) in a solution they considered suitable for low complexity and low

power hardware implementation. However, when they compared the performance of an SVM to a simpler AdaBoost classifier, they showed that the AdaBoost performed better on their data (sensitivity 98.75; FDR 0.075/h).

Comparing the RF and SVM classifier, Manzouri *et al.*[38] found that the RF performed best in real-time seizure onset detection (delay <10s) with an AUC for early seizure detection of 0.90. Furthermore, they showed that RF classification is feasible on a low power microcontroller. Comparing their solution to the *Neuropace* responsive neurostimulation (RNS) device, they found that their wider spectrum of extracted features and more advanced classification of ictal electrographic patterns came closer to a “true closed loop” intervention strategy.

2.3 Discussion

The methodologies used in the reviewed articles had a rather wide variety in source data, evaluation criteria, and validation and testing sets.

The selection of patients may affect the performance of a used algorithm. For example, whereas a lot of studies used the Freiburg dataset, it is unclear why some had to exclude patients due to artefacts[24,46], onset pattern[47], or seizure duration[48], while other studies included all. Including only patients with three or more seizures to allow for cross-validation[39] constitutes a loss in comparability to other studies, but does add to the meaningfulness of performance measures (cross-validation sensitivity). Another example from studies using the European Epilepsy database, two studies selected subjects randomly[43,49], with the only condition being a high sampling rate (1024Hz), while other studies[14,38] selected 10 patients *a priori* with a representative variety of seizure onset patterns. The latter does add to the representativeness and thus their performance gives a stronger indication of the applicability in CES. Two publications[36,37] applied entries from the *UPenn* and *Mayo Clinic*'s Seizure Detection Challenge to a wider dataset for validation, actually giving insights in the applicability of some high-performing algorithms.

Performance measures used in literature vary. Some articles report epoch-based sensitivity and specificity rates, which do not translate directly to detector performance in a clinical application. Epoch-based specificity may even lead to over-optimistic results, as rates over 95% may still falsely indicate hundreds of seizures per hour. Alternatively, FDR per day or per hour are often counted, which give a meaningful number related to the selectivity of the system and the amount of potentially unnecessary interventions. For sensitivity, most studies agree that a correct detection of a seizure occurs if the detector alerts a seizure once during the seizure, but in some studies also detections a few seconds before the marked onset are counted as true positives. Algorithms which contain adjustable thresholds or other parameters allow for a meaningful description of their performance via receiver operating characteristic (ROC) curves. The trade-off between sensitivity and FDR in that case can be represented by the AUC, which facilitates comparison between different studies.

It is likely that for CES to be successful, interventions are to be performed early during an electrographic seizure. Therefore, the detection delay between the visually annotated seizure onset and the first detection is used as a third performance measure, although often omitted. In a few cases, the delay was reduced by using a collar technique in post-processing[24,41,42], which does not apply to real-time applications of seizure detection. Instead of the detection delay, accuracy measures for the detection in the first ten seconds are sometimes presented[37,38,40]. This simplifies optimisation and facilitates the comparison of algorithm performances. The underlying assumption that the seizure does not manifest clinically within the first 10 seconds after electrographic onset, is questionable though, as the clinical onset may ensue within a shorter timespan.

Features

In several studies, a combination of features in the time and frequency domains was effective for achieving high sensitivities. Line-length and a patient-specific single spectral power have been shown to be dominant features in algorithms that focussed on linear features. Alternatively, a combination of spectral power features and power ratios has the potential to perform well with only few features.

Autocorrelation, cross-correlation, covariance between channels and other global features may improve performance, as these can utilise the repetitive and synchronising nature of seizures and were used in the best performing algorithms of the *Mayo Clinic* challenge[37]. Bipolar signals contain information for the synchronising nature of seizures. Prediction error filtering provides a simple

alternative signal to extract features, and has been shown to perform well on a single monopolar channel. Promising non-linear features from the field of brain-computer interfaces may provide additional information on the underlying state of the brain, yet they are not widely used in machine-learning approaches. Features such as lacunarity[42] may contribute to detection performance and are supposed to have low computational demand.

Features derived from the time domain signal do not require any additional processing and it has been shown that pre-processing techniques such as Fourier transform or wavelet transform can be implemented in low-power dedicated circuits[28]. The Stockwell transform, i.e. a combination of Short Time Fourier Transform(STFT) and Wavelet Transform, is expected to require more complex computations. It may have better performance as it retains phase information of the signal[24].

Classifiers

The evaluated papers demonstrated that relatively simple classifiers, e.g. RF or boosted ensembles, outperform more complex classifiers, e.g. neural networks or SVM, and are suitable for low-power applications. The RF is an ensemble learning method for classification that constructs a group of decision trees consisting of binary decisions in which each tree is trained on a subset of the training data and a subset of features. When performing the classification, each individual tree assigns a label, after which the final label is given by majority of the trees. It combines the bagging technique with random feature selection, which allows for out-of-bag error evaluation and performance calibration[50]. The RF classifier has a relative resistance to overtraining, an ability to efficiently work with large data sets, no need for normalisation of features, and it allows for the evaluation of features' importance by measuring the mean decrease in the Gini index.

Limitations

The performance indicators of the evaluated papers cannot be directly compared, because of different datasets used in the different studies. Even for studies that used the same dataset for validation, the calculation of performance indicators heavily depends on pre- and post-processing steps and experiment setup, complicating a direct comparison of performance. Mentioned delay times are not comparable, and sometimes even irrelevant for on-line detection applications if a collar technique was employed (e.g. [42]). Furthermore, we cannot assume the used datasets can adequately represent the population of sensorimotor epilepsy patients in an everyday setting. Hence, it is not safe to make a generalized assumption about the performance of the evaluated algorithms and their features. However, the outcomes provide a clear lead as to which features are most likely to distinguish between seizure onset and background activity.

Despite the intrinsic difficulties, this review aims to introduce and foster the understanding of available methods in the area of real-time seizure detection. Its contribution is towards developing a seizure onset detection system balancing computational complexity and accuracy for responsive treatment, such as CES.

Future perspective

One of the major points to bring responsive CES devices to a higher level in the therapy of epilepsy patients will be the implementation of new and more specific algorithms for seizure detection. Since the first generation of certified neurostimulation devices, a lot of studies have been published presenting increasingly more ideas to solve the problem of automatic seizure detection. It can be expected that by the need of getting better solutions to this problem, the increasing amount of available data sets and the increasing availability of toolboxes for machine learning, the amount of studies in the field will continue to expand.

3. Feature extraction and potential for seizure detection

The goal of this study is to provide a seizure detector that is suitable for online responsive intervention, such as CES, at the early stages of a seizure. Based on the literature review, a combination of time and frequency domain features is used which can be implemented in a detector using a machine learning classifier. In this chapter, the features are extracted from interictal and ictal ECoG segments to analyse their properties and potential for detecting seizures.

3.1 Methods

Before applying the features in a classifier, their behaviour is studied on a sample of 10 patients *(***Table 2***)* with sensorimotor epilepsy. All patients underwent presurgical evaluation at the University Medical Center Utrecht epilepsy monitoring unit between 2012 and 2018, using implanted cortical electrodes. ECoG was recorded for a period of 5-7 days and included in the *'RESPect'* research database with approval of the local medical ethics committee. To allow for cross-validation of a classifier later (described in chapter 4), only patients who presented at least three seizures of the same type during the intracranial monitoring period, are included.

The ECoG-data were obtained using the *Micromed* EEG system at a sampling rate of 512 or 2048 Hz. The signal was filtered in the recording system with a 0.15 Hz high-pass filter and anti-aliasing low-pass filter at 117 or 468Hz, respectively. For faster and eventually more energy efficient computation, the recordings are down-sampled to 512 Hz during pre-processing. The data was processed with *Matlab (Matlab R2018a, Mathworks Inc. MA, USA),* using the open source Fieldtrip MEG/EEG analysis toolbox[51] for pre-processing as described below.

Channel selection

The ECoG was manually annotated to identify seizure onset and artefacts, by visual inspection. The annotated data was converted to Brain Imaging Data Structure (BIDS)[52]. To limit computational demand, and respect realistic constraints of an invasive neurostimulator, six bipolar channels are selected for each patient. The bipolar channels are chosen to include different behaviours in ictal activity: for each patient two electrode pairs involved in the seizure onset (SO-SO) are included, along with two electrode pairs not involved in seizure onset (NSO-NSO) and two electrode pairs of which each has one electrode involved in seizure onset and the other electrode not (SO-NSO). In choosing electrode positions, we did not discriminate between underlying motor- or somatosensory cortical area. The bipolar electrode selection is illustrated for one patient in **Figure 2**.

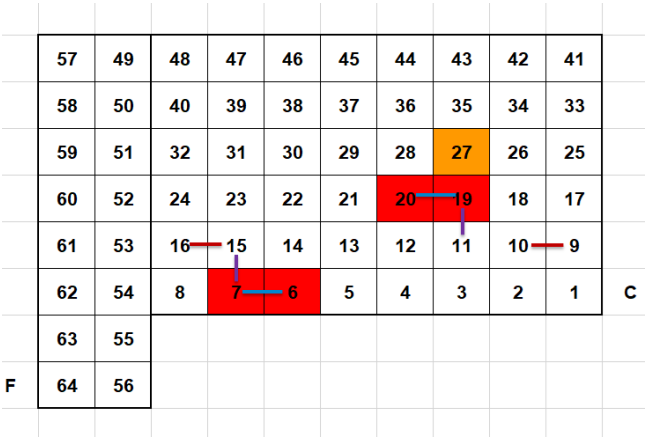


Figure 2| Schematic representation of implanted ECoG grids and channel *selection for patient RESP0295. Shown are two cortical grids (F and C) with numbered electrodes. Electrodes involved in seizure onset are indicated in red and initial spread of ictal activity in orange. Blue lines are selected bipolar channels involved in seizure onset, purple are channels that have one electrode involved in seizure onset and the other not, red lines are channels not involved in seizure onset.*

Pre-processing

Selected channels are digitally re-referenced to apply the specific bipolar montage. Data with a sampling frequency of 2048Hz was resampled to 512 Hz. Data quality is improved with a 6th order digital bidirectional Butterworth filter with a high-pass frequency of 0.5 Hz. Power-line noise is removed using a discrete Fourier transform (DFT) filter. The DFT filter fits a sine and cosine at interference frequencies (50Hz, 100Hz, 150Hz) to the signal, after which the estimated interference components are subtracted from the data.

The six filtered bipolar channels are subsequently segmented into 1s non-overlapping epochs. Epochs with prior visually annotated artefacts are removed. No epochs were removed during seizures. Additional information on the activity the patient is performing is included for later use (Chapter 4). The pre-processing pipeline is shown in **Figure 3**.

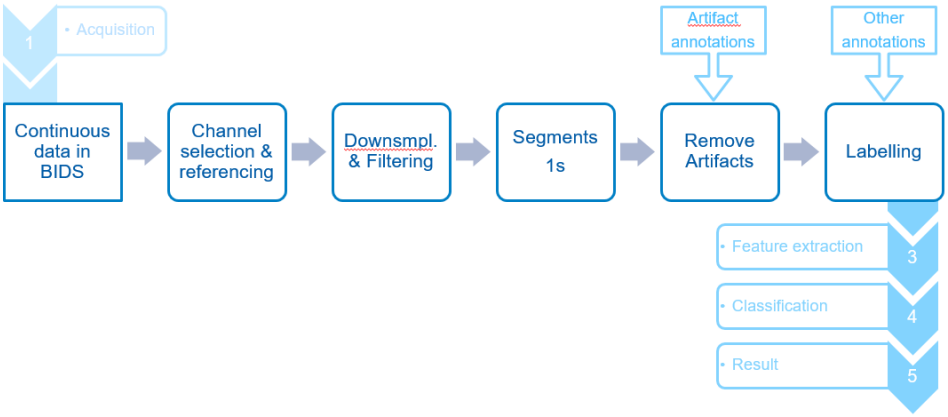


Figure 3| Pre-processing steps. *Acquired data is annotated and converted to Brain Imaging Data Structure. From this structure, bipolar channels are selected, downsampled to 512Hz, filtered with a high-pass filter and DFT band-stop filter, segmented into 1s epochs and cleared from prior visually annotated artifacts. Addittional activity labels are attached to the segments to facilitate the compilation of learning and testing sets later on (chapter 4).*

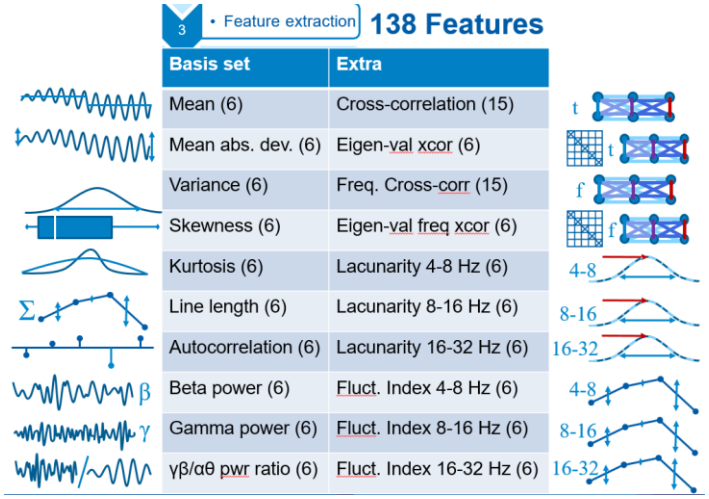
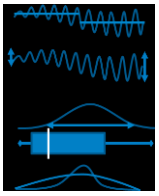


Figure 4|Overview of used feature set*. Basis set is inspired by Manzouri et al.*[38]*, Extra features include global features (cross-correlation), lacunarity and fluctuation index. Local features are extracted for each of six bipolar channels. Cross-correlation features consist of 15 combinations and 6 eigenvalues both in the frequency and time domain.*

Features

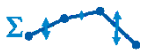
Based on the literature review (chapter 2), the following features are selected: Mean, MAD, variance, skewness, kurtosis, line length, autocorrelation, average power in beta and gamma range, as well as power ratio between higher (beta, gamma) and lower (alpha, theta) ranges. In addition, cross-correlation features are included to utilise synchronising nature of seizures, and the added value of lacunarity and fluctuation index is assessed by including them in the feature set (**Figure 4**) as well. The used features are described in detail below.

Simple (statistical) features



The four statistical moments, i.e. mean, variance, skewness and kurtosis, provide information on the location (mean), variability (variance) and shape (skewness, kurtosis) of the amplitude distribution of a time series[53]. MAD is used as another measure of statistical dispersion of the time series, more suitable for non-normally distributed data[54]. These statistical features are calculated for every epoch in each bipolar ECoG channel.

Line length feature



Line-length is a signal feature defined as the sum of distances between successive points within a certain window[55]. As such, it represents the total length of the ECoG curve within a given epoch of length *N*:

$$L = \sum_{i=1}^{N} abs[X_{t-1} - X_t] \qquad (1)$$

The line-length increases, both when the data sequence magnitude or frequency increases. It is computed for every epoch in each channel.

Autocorrelation feature

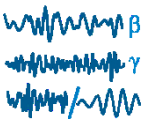
For each epoch the autocorrelation was computed using the following definition:

$$R(\tau) = \frac{E[(X_t - \mu) \times (X_{t+\tau} - \mu)]}{\sigma^2} \qquad (2)$$

where E is the expected value operator, X_t is the signal at the t time moment, μ is the mean of the signal in the 1-s epoch, σ^2 is the variance of the signal, and τ is the time lag.

The lowest value of the autocorrelation coefficient during each 1s epoch was used. The assumption is that when the seizure starts, the seizure onset pattern is rather different from the baseline ECoG, and therefore low autocorrelation coefficients are expected[14].

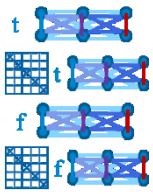
Band powers and ratio



Band powers are estimated power spectral densities (PSD) in the beta (12.5-30Hz) and gamma (30-80Hz) band. In addition to absolute spectral densities in these bands, the ratio between the sum of the power in the gamma and beta band divided by the sum of the power in the alpha and theta bands (3.5-12-5Hz) is computed. This power ratio corresponds to the first step of the computation of the epileptogenicity index[6], and has been suggested to be sensitive for low voltage fast activity onset patterns[14].

Cross-correlation features

Cross-correlation features were based on the winning submission in the Seizure Detection Challenge by Michael Hills[56]. In the time domain, time series data is normalised for every epoch. Correlation coefficients between ECoG channels and the sorted complex magnitudes of eigenvalues in the time domain are used as features.



To obtain correlation coefficients between ECoG channels and their eigenvalues in the frequency domain, power in 1-Hz frequency buckets in the range of 1-47Hz per segment is normalised for every frequency bucket (i.e. all buckets for each channel). From the normalised data, a correlation matrix is obtained. The (upper right) correlation values are used as features, as well as the sorted complex magnitudes of the eigenvalues.

By sorting the eigenvalue features, they form a so-called spectrum of the correlation matrices.

Lacunarity

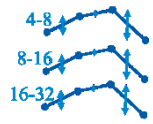
Lacunarity features are computed by first applying a DWT to split the signal in three frequency domains. DWT employs long time windows for more precise low frequency information, and short time intervals for high frequency information. A *Daubechies 4* wavelet is used, as it is considered appropriate to detect changes in ECoG signals[42]. The number of decomposition levels is chosen to be six. With a sampling frequency of 512Hz, this decomposition yields the relevant detail coefficients *(d)* representing 16–32 Hz *(d4)*, 8–16 Hz *(d5)*, and 4–8 Hz *(d6)*.

Lacunarity represents the gaps or 'lacunae' present in a given surface. In our application, it is based on the DWT detail coefficients shifted to positive values, and subsequently calculating the first *(M_1)* and second *(M_2)* order moments of mass. Lacunarity(*Λ*) then follows as described by Zhou *et al.*[42]:

$$\Lambda = \frac{M_2 - {M_1}^2}{{M_1}^2} \qquad (3)$$

Fluctuation index

The fluctuation index features use the same detail coefficients from DWT as used for lacunarity. The fluctuation index can be considered to be similar to the line length feature in a specific frequency domain, normalised for the amount of DWT coefficients in a certain scale *(N_{d4}, N_{d5}, N_{d6})*. For example, the fluctuation index in d4, representing fluctuations in the 16-32 Hz band, is calculated as follows[42]:



$$FI(d4) = \frac{1}{N_{d4}} \sum_{i=1}^{N_{d4}} abs[d4_{t-1} - d4_t] \qquad (4)$$

Statistical analysis and interpretation

For each patient, the relevance of each feature is computed by comparing the feature values of the first 20 ictal segments with the pre-ictal segments from the preceding 30 minutes. Boxplots are made comparing the pre-ictal and ictal feature values for each seizure. All ictal segment sets and pre-ictal segment sets are combined per patient to find sensitive features on the patient level. Significance of all features is determined using the Mann-Whitney nonparametric test with Bonferroni correction, for each patient. All 138 features are ranked using the absolute value of the standardised U-statistic as class separability criterion. Significant increases and decreases of feature values are assessed for all patients to see if universal patterns can be found.

3.2 Results

A total of 98 seizures was analysed, with a median of 8.5 seizures per patient (range 3-20, **Table 2**). In the separability ranking, the highest ranking features were different for each patient. Based on the top 15 features for each patient, the feature types with the highest standardised U-statistics were *variance, MAD, line-length, gamma power, beta power, power ratio, fluctuation index, time-series cross-correlation, frequency cross-correlation,* and *eigenvalue of the frequency cross correlation.* The feature types ranking among the top 15 for each patient can be found in **Table 2**.

Table 2| Overview of analysed patients and top performing feature types

Up to 20 seizures were included in the analysis per patient. RESPect numbers are references for the *'RESPect'* research database entries of the University Medical Center Utrecht epilepsy research group. FCD: Focal cortical dysplasia (ILAE classification provided if known). RAW: rhythmic alpha waves; RBW: rhythmic beta waves; RBW: rhythmic beta waves; RGW: rhythmic gamma waves; RTW: rhythmic theta waves; RS: repetitive spiking; RSW: rhythmic sharp waves; LVFA: low-voltage fast activity

RESPect number	Seizures	Age / Sex	Pathology	Grid location	Onset pattern	Top discriminating feature types
295	**14**	31 / M	Unknown (FCD 1a)	L Frontocentral / temporal	*RGW*	*Line-length, gamma power, eigenvalue freq. cross-correlation, freq. cross-correlation, power ratio*
733	**3**	9 / M	Perienatal ischaemia	L Frontocentral / interhemisph.	*RBW*	*Line-length, fluctuation index, variance, MAD*
545	**4**	9 / M	FCD 2	L Central / Interhemisph.	*RSW*	*MAD, variance, freq. cross-correlation, eigenvalue freq. cross-correlation, time-series cross-correlation, power ratio*
529	**4**	16 / F	Trauma	R Central	*RAW, RSW*	*Line-length, gamma power, beta power, fluctuation index, variance, MAD*
621	**20**	18 / F	FCD 2b	L Central	*RBW, RGW*	*Line-length, power ratio, gamma power, fluctuation index, variance*
677	**7**	17 / M	FCD 2b	L Central	*RGW*	*Fluctuation index, power ratio, freq. cross-correlation, MAD, variance, eigenvalue freq. cross-correlation*
561	**10**	28 / M	unknown	L Central / interhemispheric	*RBW*	*Line-length, freq. cross-correlation, power ratio, eigenvalue frequency cross-correlation, gamma power*
608	**6**	24 / M	FCD 2b	L Cental / temporal	*RS, LVFA*	*Line-length, eigenvalue freq. cross-correlation, power ratio gamma power, fluctuation index, beta power*
294	**10**	35 / F	unknown	L frontal/ frontocentral	*RS*	*Line-length, gamma power, beta power, fluctuation index, eigenvalue freq. cross-correlation*
699	**20**	13 / M	FCD 2a (2b)	R frontocentral	*RTW, RGW*	*Line-length, power ratio, gamma power, fluctuation index, variance*

An example patient

For the example patient 295, the *mean* and all *lacunarity* features showed no significant differences between the pre-ictal and interictal epochs sets. MAD and variance show co-varying significant increases and decreases of the median values in all channels. *Kurtosis* shows a significant decrease in channels not involved in seizure onset (NSO-NSO), whereas *skewness* shows a significant change in channels involved in seizure onset (SO-SO). The *line-length* feature has a significant increase in all six channels. *Autocorrelation* shows a significant decrease in NSO-NSO channels, and an increase in one SO-SO channel. *Gamma power* and *Power rate* are significant in all channels and show the highest increase in SO-SO channels. *Beta power* mostly has a significant decrease, although it increases in one SO-SO channel. *Fluctuation index* decreases in most of the channels in all three bands, while in the higher band (16-32Hz) one SO-SO channel shows a significant increase.

Among the global features, the *time-series cross-correlation* feature was significantly increased or decreased in five correlations between channels of which one channel had one electrode involved in seizure onset and the other not (NSO-SO), and a significant increase in one correlation between an SO-SO channel and an NSO-NSO channel. One *cross-correlation eigenvalue* showed a significant, yet minor, decrease. *Frequency cross-correlation* showed a significant decrease in all cross-correlations, except the cross-correlation between the two NSO-NSO channels. The lowest five sorted *eigenvalues of the frequency cross-correlation* showed a significant decrease, while the highest eigenvalue in the spectrum decreased. Patient level significance for this example patient is illustrated in **Figure 5**.

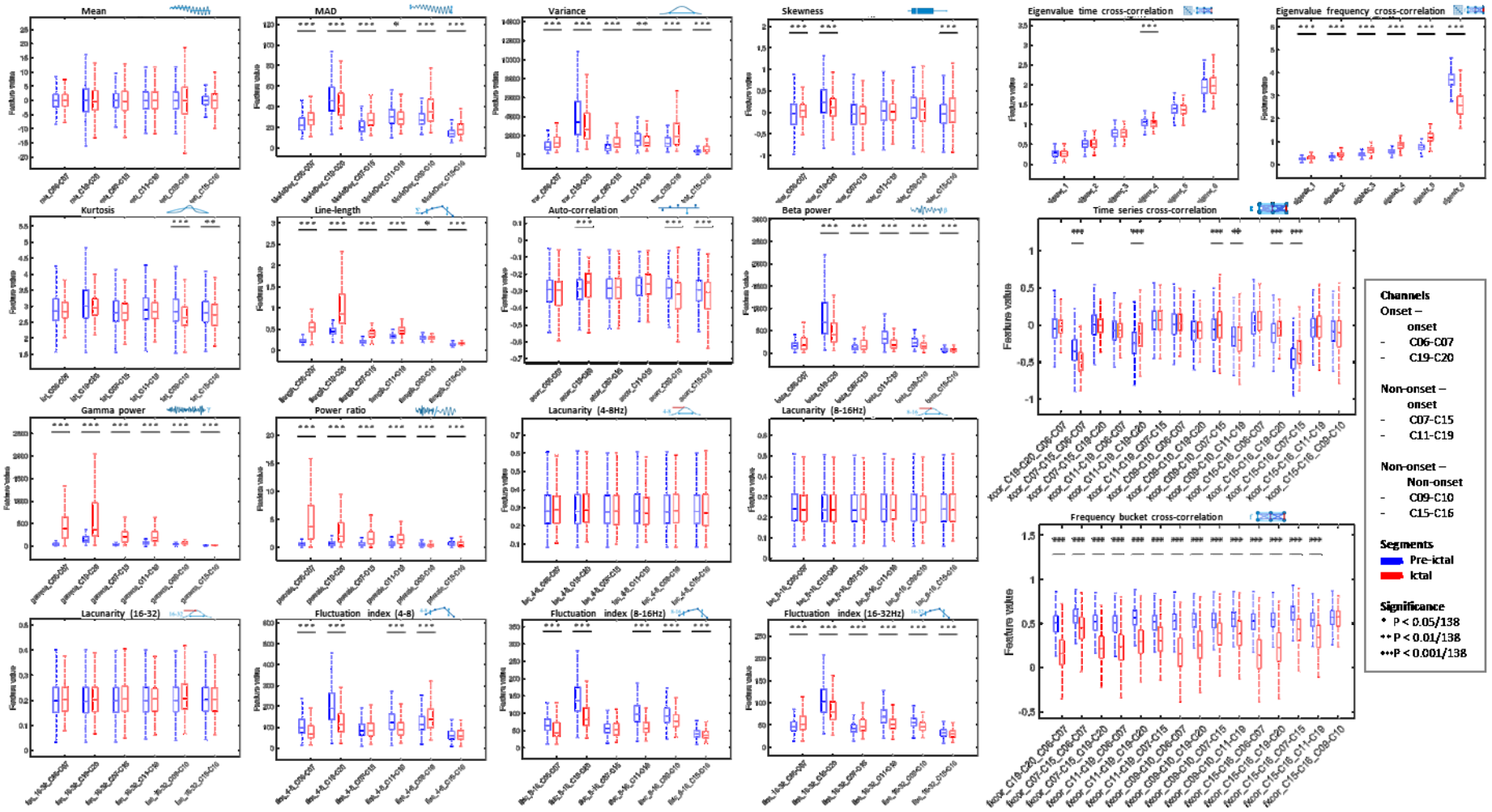


Figure 5 | Comparative boxplots of all features for example patient 295. Comparing pre-ictal feature values with ictal feature values. Variance and MAD show the same behaviour. Skewness and kurtosis show minor yet significant changes. Line-length feature values show a significant increase, especially in the SO-SO channels. Gamma and beta power, as well as the power ratio show significant increases. Lacunarity has no significance for this patient. Fluctuation index decreases in most channels. Time series cross-correlation has significant increases and decreases in different correlation pairs. Frequency bucket cross-correlation shows an overall decrease of the cross-correlation, which is also clearly reflected in the decreas of the highest eigenvalue. (Further observations can be found in the text body above)

Aggregated results of all patients

When compiling all the results of the 10 patients (Figure 6), we see that the insignificance of the *mean* feature is universal for all patients. *Lacunarity*, however, does show significant changes in seven patients. The detail coefficient representing the 4-8Hz band only has significant lacunarity changes in one patient (608). The lacunarity of detail coefficients representing 8-16Hz and 16-32 Hz change significantly for six and seven patients respectively.

MAD and *variance* features co-varied in all patients, i.e. they show the same significant increases and decreases across all channels in both features. For one patient (677), there was only one channel in which the variance and MAD changed significantly. *Kurtosis* and *Skewness* were not significant for this patient. The *autocorrelation* feature decreased significantly in both NSO-SO channels for four patients (295,561,294,699). For one patient (529), autocorrelation increases in all channels except one NSO-SO channel.

The *fluctuation index* is significantly increased across all bands in at least one channel of each type for three patients (733,529,608). It also shows significant decreasing values across all types of channels and bands for the seven other patients, along with some significant increases, predominantly in the higher frequency band.

Line-length increased significantly in all channels for seven patients, and in a majority of the channels for the other three (545,529,621). For one patient (545), it did not increase significantly in both the SO-SO channels, but it did increase in the other channel types. *Gamma power* did also not increase significantly in patient 545's SO-SO channels, nor did it increase in the SO-SO and NSO-SO channels of patient 677. Otherwise, it showed a general significant increase among the channels, except for one NSO-NSO channel in patient 621, in which it actually decreases. *Beta power* shows general increase for two patients (733,608), but there are channels with a significant decrease for four patients (295,621,677,699). In patient 677 this significant decrease occurred in both of the SO-SO channels. *Power ratio* increased significantly in all SO-SO for all patients and all other channels for five patients (733,677,561,608,294). A significant decrease occurred for two patients (295,699) in SO-NSO channels, and in a NSO-NSO channel for patient 621.

Among the global features, the *time-series cross-correlation* between both SO-SO channels was significantly increased for two (677,608), and decreased for four patients (545,529,561,294). Between different types of channels, both significant increases and decreases occur. One patient (621) has no significant change in cross-correlation, except for one SO-SO/SO-NSO correlation. *Cross-correlation eigenvalues* showed no significant changes for two patients (621,699). The highest sorted eigenvalue was significantly decreased for four patients (733,677,561,294), whereas it was significantly increased for two (545,529).

Frequency cross-correlation feature is decreased in most correlation pairs for nine patients. Patient 621 has fewer significantly decreasing correlation pairs and two increasing correlation pairs, of which one is between both NSO-SO channels. The lowest five sorted *eigenvalues of the frequency cross-correlation* showed a significant decrease in seven patients, and the highest eigenvalue in the spectrum decreased significantly for all but one patient (621).

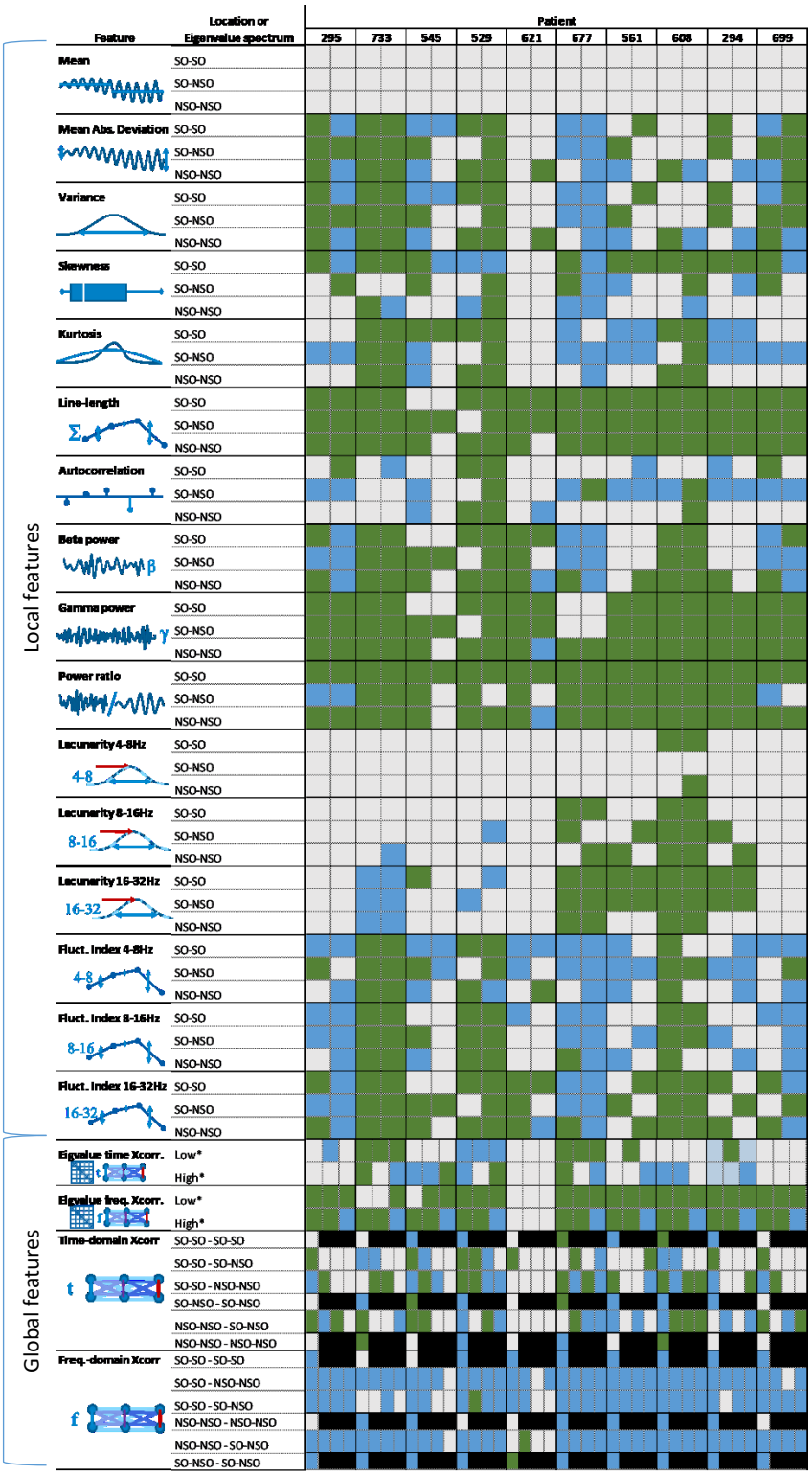


Figure 6 |Overview of significant (P < 0.01/138) changes in feature levels. Green represents a significant increase of the feature, blue a significant decrease of the feature value, grey represents no significant change. The 16 ***local features*** *types are extracted from six bipolar channels for each patient. Local feature channels are grouped in rows by their location's involvement in seizure onset (SO-SO, NSO-NSO, NSO-SO). MAD and variance show the same behaviour in all channels. Line-length, gamma power, power ratio and show relative consistent increases in most channels. For* ***global features****, the eigenvalues are in increasing order (*), with the lower three and higher three shown in two rows. Cross-correlations are grouped by the involvement of each of the correlated channels in seizure onset. Eigenvalues of the frequency cross-correlation show relative consistent decrease of the highest eigenvalue along with an increase of the rest of the spectrum. Frequency cross-correlation is decreased significantly in most channels. (Further observations can be found in the text body above.)*

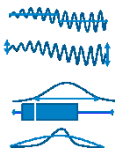
3.3 Discussion

In this chapter, we described the seizure extraction method and compared the feature values from the interictal and ictal ECoG epoch sets to analyse the features' properties and potential for detecting seizures. The general idea is that feature values that change significantly during seizures, and more specifically during seizure onset, will be useful in discriminating between interictal and ictal segments by our classifier later on. For all features that show significant differences between the ictal and pre-ictal epochs, it is important to realise that this does not directly translate to predictive power of the features. As the primary focus is on the behaviour and discriminative power of the features, each feature type is shortly discussed below.

Simple (statistical) features

None of the *mean* features was ever significant. This can be attributed to the used AC amplifier and pre-processing steps, such as the bipolar montage. As it is never significant, it is unlikely to be of any added value in a classifier.

The similar behaviour of *variance* and *MAD* could be expected, as both are measures of dispersion of the time series. Variance and MAD increased during seizures in several channels, which represents the volatile nature of the ictal ECoG. However, in several channels these dispersion measures actually decreased. Although this might be due to low-amplitude characteristics of certain seizure onset types, it is more likely caused by the bipolar montage. Using bipolar channels cancels out synchronous activity with similar amplitudes in certain electrode combination. This accounts for some of the decreased variance levels.



For *skewness*, it is actually not relevant to consider increases distinct from decreases, as this simply depends on the polarity of the montage. Although skewness and kurtosis were never in the top 15 features, they do seem to provide information in some channels on the shape of the distribution that may contribute to the discrimination between ictal and non-ictal epochs. Most notably, skewness was differed significantly in all SO-SO channels, except for one patient (621).

Line length feature

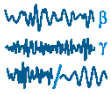
Line-length is expected to increase, both when the data sequence magnitude and/or frequency increase. The general increase of the *line-length* in most channels indicates it is a strong candidate for classification. The increase was not expected in channels selected to not be involved in seizure onset (NSO-NSO), but it appears the gamma power increase in those channels is strong enough within the first 20 seconds of electrographic onset. Line-length features scored consistently among the top 15 features, and are expected to give an important contribution to classifier performance. Channels where line-length did not work well, such as the SO-SO channels of patient 545, had a lot of interictal spiking in the onset channels. As such, line-length is less capable of discriminating between ictal an non-ictal epochs.

Autocorrelation feature

The autocorrelation feature is among the hardest to interpret. As it is based on the assumption that the seizure onset pattern is different from the baseline ECoG[14], it is conceivable that autocorrelation only drops significantly in a few epochs at the start of a seizure, and otherwise has rather constant values. It shows this drop mainly in SO-NSO channels. As it takes only the minimum value within an epoch, information on the actual autocorrelation characteristics get lost during feature extraction. This may account for the varying behaviour. Nevertheless, it does seem to provide some information for all patients, and may be of added value in a classifier.

Band powers and ratio

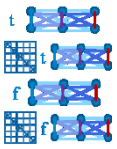
All frequency band power features generally showed a convincing increase. It is likely that higher frequencies were relatively unaffected by the bipolar montage, as lower frequencies are more likely to achieve phase synchrony during seizures. It was suggested that the combination of bipolar channels and power ratio could adequately discriminate between ictal and non-ictal epochs based on amplitude similarity and phase synchrony[43].



The extracted features used pre-defined frequency bandwidths to compute band power. It is possible that for some patients band power features would perform even better if the bandwidths were adjusted to their seizure type. Still, many features based on these fixed bands rank among the top 15 features for most patients. As such, they show a strong discriminating potential between ictal and non-ictal epochs.

Cross-correlation features

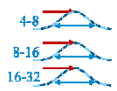
The *cross-correlation in the time-series* did not perform very consistently across patients. It was suggested that zero-lag cross-correlation may only really increase towards the end of the seizure[57], which may explain the lack of changes in cross-correlation coefficients for many channels. We should also note that due to the bipolar montage, our channels already represent the difference in potential between two cortical electrodes. As electrodes become more synchronous, the bipolar signal will drop close to zero and so will their cross-correlations with other signals. In the time domain, there is no distinction between increases and decreases of the cross-correlation, as negative correlations simply depend on the polarity of the montage. In the *frequency domain*, however, feature values tend to be positive, and this feature shows a clear behaviour across all patients. The widespread strong decrease of cross-correlation coefficients in the frequency domain between these bipolar channels is remarkable. It implies that during seizures the distribution of power across 1Hz buckets becomes less similar in nearly all bipolar channels.



This is also adequately captured by the eigenvalues of the correlation matrix. Each eigenvalue reflects the correlations between all six ECoG channels, but the largest amount of correlation is represented by the highest eigenvalue. The increase in the rest of the spectrum also contains information about the changing correlations. As such, the spectrum indeed allows for a compact assessment of the evolving correlation structure.

Lacunarity

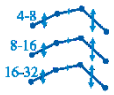
Lacunarity is among the lowest ranking features for most patients. The poor performance may be due to the computation of the feature during which the detail coefficients is shifted to positive values. As this shift depends on the minimum value of in the epoch, the resulting feature value may depend more on this minimum than on the actual lacunarity. Extracting the feature using a fixed offset, would require prior knowledge of the range that each detail coefficient may have, which would it less applicable in an online detector.



With its limitations, however, it does seem to capture some information for a subset of patients, mostly in the detail coefficient representing the higher (16-32Hz) band.

Fluctuation index

Although the fluctuation index can be thought of as a decomposition of the line-length feature in three frequency bands, it does not seem to capture the same information as the line-length feature. Whereas line-length has a significant increase in most channels, the fluctuation index shows a lot more decreases. This can be attributed to effects of the DWT that precede the extraction of the fluctuation indices: of the decomposition, only the coefficients that represent 4 to 32Hz are used to compute the fluctuation index. Thus, fluctuations in the gamma band are largely excluded. The 16-32Hz fluctuation index behaves similarly to Beta power, so the two are likely to contain the same information.



Limitations

The selection of bipolar channels is inherently subjective and patient-dependent. Although a careful selection took place to ensure the use of artefact-free channels that capture different combinations of involvement in ictal activity (i.e. both involved in seizure onset, neither involved in seizure onset, and only one involved in seizure onset), this still does not guarantee comparable channels across different patients. The goal of including these different combinations of involvement, was to strive for capturing as much information in the bipolar channels as possible. The variation in feature behaviour among channels in each patient seems to confirm that this was successful to some extent. In choosing electrode positions, we did not discriminate between underlying cortical areas, nor did we take into account in which areas would be stimulated if the patient would actually receive a closed-loop CES device. In an actual CES implant, these factors might constrain electrode locations.

For some patients, several features did not perform as good as for other patients. Several factors can play a role in these differences. Besides the mentioned limitations in channel selection, different patients also produce different onset patterns (**Table 2**). The amount of seizures and variability between ECoG characteristics between seizures for the same patient, can also reduce significance of the differences between ictal and pre-ictal activity. Lastly, the baseline ECoG before each seizure may be in a specific sleep state that is harder to distinguish from seizure onset.

In creating ictal and pre-ictal epoch sets, stages of ictal activity may be included in the ictal epoch set that go beyond what can be considered seizure onset. However, reducing the amount of epochs even further would impede the possibility of achieving significant results. The use of pre-ictal epochs as opposed to inter-ictal epochs not closely preceding a seizure, may give a non-representative view of the baseline ECoG, as there is increasing evidence of the existence of a pre-ictal state[58,59]. For the application of a responsive CES device, distinguishing between ictal and pre-ictal seems the most relevant, when targeting seizure onset specifically.

Comparing interictal ECoG with early ictal ECoG epochs using a statistical test like the Mann-Whitney nonparametric test involves certain assumptions about the distribution of the feature values, and thus the underlying data. As ECoG signals are nonlinear and non-stationary in nature, the assumption of independent and identically distributed observations does not apply. Incorporating multiple seizures and different interictal segments does provide a moderate compensation for the correlated and non-stationary data. When using these features in a machine learning classifier, more complex decision boundaries will emerge that do not necessarily require this assumption to hold true. Especially not when using classifiers that apply a bootstrap aggregating (bagging) technique[60].

Perspectives for classification

The used 138-feature set, including sixteen types of local features and four global features, have a potential for discriminating between ictal and pre-ictal epochs. Variance, line-length, gamma power, beta power, power ratio, fluctuation index, time-series cross-correlation, frequency cross-correlation, and eigenvalue of the frequency cross correlation are the most promising feature types in this set. The combination of the line-length feature with power band features and global features could be a promising basis for classification. Other included features may complement these by adding some additional discriminative power.

Although multiple features may have very significant differences between ictal and pre-ictal epochs, a classifier may only use one of them, if the actual information the features are based on is the same. The most obvious example is the variance and mean average deviation, which both represent the dispersion. Less explicit confounders are conceivable, as e.g. delta power and line-length both increase when fluctuations in the delta band increase.

4. Classification and validation

The features from the preceding chapter are used to implement a detector based on a RF classifier. The patient-specific classifier is trained and tested on patients' data and compared with a method similar to one of the methods used by the only medically approved responsive neurostimulator (*Neuropace* RNS).

4.1 Methods

The early seizure detection algorithm is trained and tested on retrospective ECoG data from ten patients with sensorimotor epilepsy. We used the same set of seizures from the ten patients as described in Chapter 3 (**Table 2**) as a starting point for the training set for training each patient-specific classifier. ECoG recordings containing seizures are split in blocks, each containing at least one seizure and a varying amount of pre-ictal and post-ictal data. Blocks with multiple seizures are split so that in every block there is one seizure. Post-ictal data is excluded for 20 minutes after the seizure offset.

To obtain the chance of early detection without the use of overlapping windows, which would introduce extra computational demands, feature sets are computed using non-overlapping 1s epochs, as described in Chapter 3.2. Subclinical seizures are removed from the training dataset. As in chapter 3, epochs are either labelled ictal or non-ictal.

It is important that the classifier can distinguish between ictal activity and different sleep stages. Early NREM, late NREM and REM stages each have their own characteristics reflected in ECoG, which might resemble ictal activity in some regards. As we are dealing with sensorimotor cortex, a sudden change in mu-rhythms may also resemble ictal activity. Therefore, additional interictal blocks are included in the training set for each patient and labelled as non-seizure: at least 10 minutes of non-REM or early sleep, 10 minutes of REM sleep or late sleep, and 10 minutes of performing a controlled motor task or other dexterous activity.

Cross-validation

Because the number of seizures is low in some of the included patients, seizure-level leave-one-out cross validation is performed while training the classifier for each patient. In this process, one seizure and its preceding pre-ictal data is left out for testing and the classifier is trained using the remaining seizures, complemented with the additional interictal blocks. This is repeated with each seizure left out once for testing.

From the cross-validation, the sensitivity for early detection is determined by whether each seizure was detected within the first 10 second using the classifier. The end time of the first epoch to be detected successfully is considered the detection delay for that seizure. The median detection delay and delay range are used as performance indicators. The cross-validation also provides an estimate of the FDR for all the detections occurring in the left out pre-ictal data. In the end, the classifier with the best performance over the entire data is selected.

Testing dataset

The available literature rarely performs additional testing and often accepts relatively FDRs (see Chapter 2). In order to give a good estimate of the performance of the detector, we choose to perform an additional false positive test with a held out testing set. For the testing dataset, around 24 hours of interictal data from each patient is used as a testing dataset. The testing set is used to get a FDR for each patient-specific algorithm.

Random Forest Classifier

The number of trees is set to 100. Higher numbers of trees were tested but did not increase the accuracy of classification significantly. The number of features randomly selected at each node is set to $\sqrt{N_{\text{features}}}$ rounded up, i.e. twelve features at each node. The Gini coefficient[61] is used as branching index in growing each decision tree of the RF. The importance of each feature is computed based on the decrease of this Gini coefficient, eliciting which features are more active.

Reference algorithm: comparison with existing neurostimulator detector

The *Neuropace* RNS system uses any (up to two) of three detection tools operating on 1 or 2 channels to detect seizure onset[62]: the half-wave tool segments the electrographic signal at local minima and maxima resulting in half-waves representing frequency components; the area tool measures the overall power of the signal; and the line-length tool employs the sum of distances between successive points to identify changes in both amplitude and frequency.[63] Since precise assessment of the *Neuropace* RNS system is not possible[64], the line-length based thresholding classifier as estimated by Manzouri *et al.*[38] is implemented as a reference algorithm to compare performance with our algorithm.

For this approximation of the algorithm, the line-length feature as described in Chapter 3.1 is normalised by z-scoring, and a threshold is set that optimises sensitivity and FDR. A logical 'or'-function was used to combine the results of the two SO-SO detection channels. The same cross-validation is used for the line length algorithm, as was used for the RF classifier to assess the sensitivity and obtain an estimation of the FDR, and the testing set is used to get a realistic FDR.

Performance indicators

Sensitivity, defined as the ratio of correctly detected seizures to the total number of seizures, is used as measure for the ability of the classifier to detect seizures. Early seizure detection (<10 s) sensitivity is used to measure the ability to actually detect seizure onset.

FDR as a tool for measuring the ability of the classifier to avoid false positive detections, defined as the number of false detections made by the classifier in an hour of testing data. Both the FDR from cross-validation and from the held out testing set are used to evaluate the performance.

4.2 Results

The top five dominant features for each patient were of the feature types *beta power, gamma power, power ratio, line-length, variance, MAD, fluctuation index (8-16Hz, 16-32Hz), time series cross-correlation, frequency bucket cross-correlation,* and *eigenvalue of the frequency cross-correlation.* The properties of classifiers in cross-validation generally agreed based on gini-indices from each iteration of the cross-validation (shown for one patient in **Figure 7**)

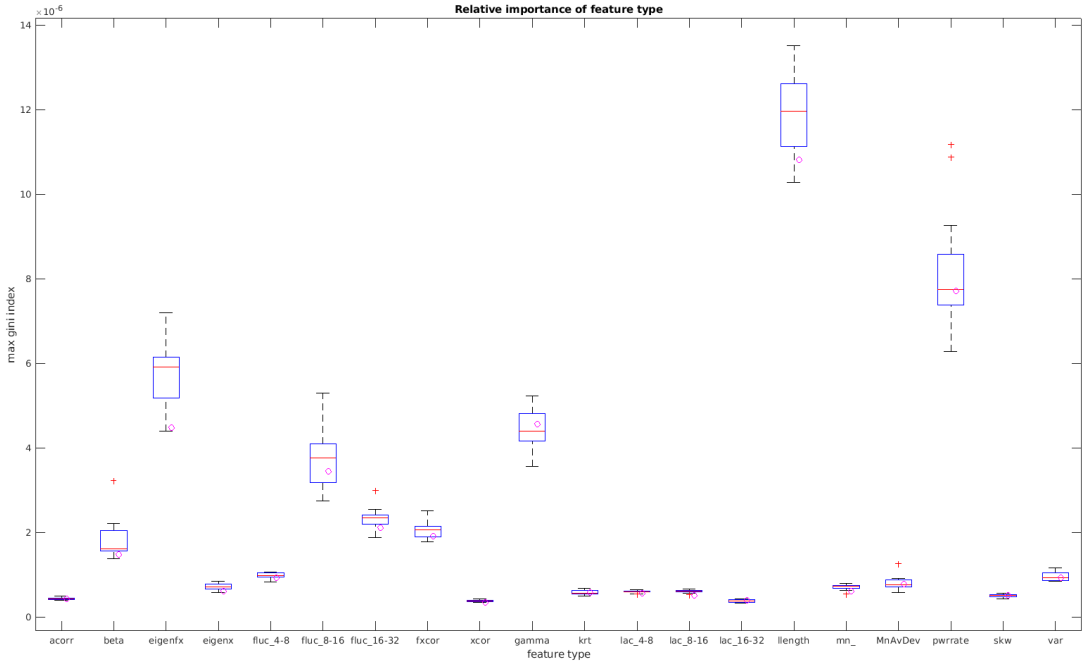


Figure 7 \| Relative importance of features grouped per feature type for patient 295*. In this example patient, line-length, power ratio, gamma, fluctuation index (8-16Hz), and eigenvalues of the frequency cross-correlation were dominant feature types in the classifiers during cross-validation. The gini-index of the combined classifier is shown as a circle, and shows the same top 5 dominant features.*

The RF classifier achieved a sensitivity of 100% and a mean early sensitivity (<10s) of 98%. FDR in both the cross-validation and the testing set was 1.45/h and 1.53/h respectively; being under 2.5/h for most patients, except for patient 294 and 677. The performance of the detectors is given in **table 3**. The line length algorithm had a sensitivity of 98% mean early sensitivity of 81%. It is possible to increase this sensitivity by lowering the threshold, but it would drastically worsen the FDR which has an average of 4.43/h in the testing sets. The mean delay was 3.9s for the RF classifer as compared to 6.1s in the line length algorithm.

Table 3 \| Performance of random forest classifier, compared with the line-length algorithm..
FDR: False Detection rate; CV: Cross-Validation; Test: Testing set; RESP: references for the RESPect database.

Patient (RESP)	**Full feature set + Random Forrest Classifier**				**Reference algorithm**			
	Sensitivity (<10s)	**FDR_{cv} (/h)**	**FDR_{test} (/h)**	**Median delay (min-max)**	**Sensitivity (<10s)**	**FDR_{cv} (/h)**	**FDR_{test} (/h)**	**Median delay (min-max) (s)**
295	0.92	2.1	1.8	7 (3-18)	0.89	4.31	7.15	8 (4-17)
529	1.00	0.30	0.40	4 (2-8)	0.88	3.82	4.21	6 (2-16)
545	1.00	0.26	0.34	2 (1-6)	0.25	4.1	3.21	11 (4-18)
733	1.00	0.09	0.38	1 (1-3)	1.00	2.23	5.21	1 (1-3)
294	1.00	3.01	2.53	5 (1-8)	.83	2.11	3.66	7 (2-12)
621	0.93	1.83	2.18	7 (4-15)	.88	3.32	5.21	9 (4-15)
677	1.00	4.01	5.21	3 (2-6)	.94	4.32	9.31	4 (2-11)
561	1.00	1.32	1.12	3 (1-7)	0.73	1.29	2.5	6 (2-13)
608	1.00	0.69	0.23	3 (1-8)	0.83	0.71	0.81	5 (1-11)
699	.95	0.93	1.05	4 (2-11)	0.90	1.35	3.03	4 (3-12)
Mean	**0.98**	**1.45**	**1.53**	**3.9**	**0.813**	**2.76**	**4.43**	**6.1**

4.3 Discussion

The aim of this chapter was to implement a patient-specific detector using a broad set of local and global features (chapter 3) in a RF classifier. The detector was compared with a reference algorithm on clinical data from 10 patients with sensorimotor epilepsy. Performance of the RF classifier was generally better than that of the line-length algorithm. With an early detection (<10) sensitivity of 0.98, and an FDR around the 1.5 /h, the RF algorithm shows a great improvement over the use of the line-length algorithm with an early detection sensitivity (<10s) around 0.82 and FDR in the order of 4.4/h. The detection delay of the RF classifier had an average of 3.9 s, which is competitive with other on-line seizure onset detection methods that do not employ post-processing techniques to reduce the detection delay[14,65].

Using the Random Forest classifier

The RF classifier was used, because of its few required parameter optimizations, the ability to efficiently work with large data sets, its resistance to overspecialisation and the lack of need for feature normalisation. Parameters, such as the amount of trees, could easily be set to a satisfying number. After trying some higher numbers without significant improvements, 100 trees were enough to get a stable classification result. The suggested[50] amount of randomly sampled predictors to consider at each split set at $\sqrt{N_{\text{features}}}$ requires no fine-tuning either.

Not all features in the feature space were relevant. Although it is expected that some features may be interchanged for one another by the classifier if they are based on the same characteristics, it is likely that the results would have been similar without including the *mean* and *lacunarity* features. A feature reduction step could be added, to create a lighter and perhaps more efficient classifier. However, doing feature reduction properly requires a rather slow iterative process as ideally one should only remove a single feature from the space at a time, to see how it impacts the others.

Comparison with line-length algorithm

The implementation of line-length algorithm does not mimic the workings of the *Neuropace* RNS device completely. The *Neuropace* RNS can use up to two detectors in two channels, which can also be set to use the half-waves tool or the area tool[66]. Of these three, the line-length tool is considered the most effective, because it sensitive for both low-amplitude fast and high-amplitude slow activities during the course of a seizure[28]. For one patient (**545**), the line-length algorithm was performing remarkably worse than for the others, which could have been predicted based on the insignificance of the line-length feature in the SO-SO channels as described in Chapter 3.2. It is possible that the *Neuropace* half-wave detector would have been more suitable for these channels, as e.g. the power ratio had a strong impact in the RF classifier for this patient.

The line-length feature plays an important role in the RF classifier. However, the addition of PSD features, variance, fluctuation index and global features, in combination with the light yet versatile RF classifier have shown to be a good seizure onset detection algorithm, possibly bringing the field closer to a true closed-loop intervention strategy.

5. General discussion

This thesis set out to find improved approaches for highly specific and fast seizure onset detection for a new generation of intelligent implantable responsive CES devices, which may become an effective alternative to epilepsy surgery in the near future. It aimed at finding algorithms that have promising characteristics for seizure onset detection, and combining the best aspects of those algorithms, to ultimately test the performance of a combined algorithm on clinical ECoG data from patients with sensorimotor epilepsy.

Machine learning approaches have been on the rise in the last decades, providing plenty of tools to classify data such as ECoG signals based on many more extracted features. Finding the most promising directions to take is no straightforward task, as outlined in chapter 2 of this thesis. The methodologies used in the reviewed articles had a rather wide variety in source data, and validation and testing sets. It became clear that performance indicators of the evaluated papers could not be directly compared. During the writing of this thesis, M. Dümpelmann published an extensive topical review on early seizure detection for closed loop direct neuro-stimulation devices in epilepsy[67]. In this review, he goes as far as to only name the performance metrics in the literature overview, without providing the achieved numbers, simply because there is no consensus on what should be counted as a true positive when calculating the sensitivity and other metrics.

Our approach

In the end, we decided on a set of features by critically evaluating the literature, not only looking at the used features and classifiers, but also at the used methodology: as to patient inclusion criteria and the potential application in actual on-line seizure detection. We picked out a feature set that could combine the proven strong performance in seizure onset detection for a variety of seizure onset patterns[14,38], with the benefits of global features with excellent performance in a benchmarked competition[37,56].

Extracting these features from clinical ECoG data of patients with sensorimotor epilepsy, and analysing the change of the feature values during seizure onset, showed that patient-specific algorithms are indeed required to possibly achieve a performance good enough for a true closed loop system. The variability between patients can only partly be explained by their differing seizure onset patterns. The selection of channels is a crucial step in the process, which can also be approached more analytically. Truong *et al.*[68] incorporated an automatic channel selection engine as a pre-processing stage to a seizure detection procedure, achieving state-of-the art performance with such an automated detection step.

In our case, pairing the selected 138 features with an RF classifier, yielded promising results. Our performance metrics cannot be directly compared to other studies, because of the same major limitation of definitions, used data and methodology. However, the comparison with the (sometimes considered gold standard[36]) line-length algorithm does show a significant improvement on our data. While our dataset was newly created for this research, it could be the starting point of a benchmarking set used especially for seizure onset in the sensorimotor cortex, which is a highly relevant target group for responsive CES, due to their often inoperable focal epilepsy.

Before the dataset can be used as a true benchmarking set, some important aspects of the data still have to be validated. There is an inherent subjectivity in the marking of seizure earliest electrographic change. A benchmarking set would preferably have these onsets annotated by at least two epileptologists with a systematic approach. The same applies for the channels involved in seizure onset. If channels are to be manually selected, the highest care should be given to mark these

channels as objectively as possible. Eventually, more patients can be added to the benchmarking set, as part of the *RESPect* database, which can help to draw stronger conclusions as to the external validity of the used performance metrics.

Now the testing and validation yielded promising results, steps from algorithm development to its implementation in low-power hardware can be considered. The application of seizure onset detection for responsive CES will have to be realised in a hardware device with certain restrictions related to power consumption, memory, and runtime. The first step towards this will be a proof of concept of the algorithm in an on-line application during epilepsy monitoring with implanted subdural electrodes in September 2019.

Outlook

Researchers of the University Medical Center Utrecht epilepsy group are planning to carry out an analysis of the electrographic characteristics of sensorimotor epilepsy. This could potentially give direction to further development of seizure onset detection algorithms, as their findings could be taken into account to identify prevalent seizure onset patterns in the target population, as well as predicting potential challenges in automated sensorimotor seizure onset detection. This could possibly help to make more tailored decisions in setting up a feature set.

The choice for an RF classifier remains unchallenged for now, as no other classifier has been shown to have superior performance[67]. However it is conceivable that with the rise of convolutional neural networks, along with the rise of implants that can collect large amounts of ECoG data, these deep learning approaches may take over. Hügle et al.[69] already made a proof of concept for an implantable CNN-driven CES device.

The closely related field of seizure prediction may provide new opportunities. In this thesis, prediction algorithms, which try to detect changes minutes before the actual clinical seizure occurrence, were disregarded, because sensitivity and specificity values are in an entirely lower order[58]. However, the incorporation of features likely to represent the pre-ictal state, could be an interesting addition to the feature space in a seizure onset detector, as they may indicate the probability that a certain change in other feature values actually represents a seizure onset.

With the continuing expansion of the field, exemplified by the start of a clinical trial in the University Medical Center Utrecht (REC2Stim), the availability of data and interest in the field are expected to increase, moving the field of online seizure onset detection for responsive stimulation forward.

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Verantwoording
Klinische Specialisatiestage

Technical Medicine

Paul L. Smits - Augustus 2019

Mijn afstudeerstage loopt langzaam maar zeker richting een afsluiting. Een jaar van vele kleine maar ook enkele grote uitdagingen, waarin ik veel heb geleerd en in mijn persoonlijke ontwikkeling verder ben gegroeid. Ik voel mij inmiddels een echte Technisch Geneeskundige, maar tegelijkertijd besef ik maar al te goed hoe veel meer er nog te leren valt. De kennis die ik heb opgedaan het afgelopen jaar is wellicht domein-specifiek, maar de inzichten en vaardigheden zullen mij ook breder van pas komen.

In dit verslag zal ik ingaan op de persoonlijke leerdoelen die ik in de beginfase van mijn stage heb opgesteld en hoe ik me met deze leerdoelen heb beziggehouden. Ook zal ik de activiteiten noemen welke niet direct gerelateerd zijn aan mijn leerdoelen of hebben bijgedragen aan mijn onderzoeksverslag, maar welke desalniettemin hebben bijgedragen aan mijn persoonlijke ontwikkeling.

Medisch handelen en werkterrein

Mijn eerste leerdoel was om beter bekend te raken met het medisch handelen van de neuroloog en klinisch neurofysioloog. Wat ik daarbij wilde bereiken is een inzicht in het handelingsperspectief van de specialist, maar ook zeker een duidelijker beeld van het perspectief van de patiënt. Hierbij richtte ik mij op een achttal ziektebeelden waarvan ik verwachtte hier in de kliniek een goede kans te hebben om er meer over te leren:

1. Epilepsie en kortdurende wegrakingen
2. Stoornissen van het bewustzijn / Comateuze patiënt
3. Stoornissen van de slaap
4. Cerebrovasculaire ziekten
5. Corticale functiestoornissen en dementie
6. Liquorcirculatiestoornissen
7. Neuromusculaire aandoeningen
8. Trauma van het centrale en perifere zenuwstelsel

Uiteraard heb ik hierbij vooral met het eerste ziektebeeld te maken gehad, aangezien ik direct betrokken was bij de onderzoeksgroep epilepsie. Epilepsie behoorde tot mijn dagelijkse focusgebied. Door mee te lopen op de polikliniek en de *first-seizure clinic*, heb ik veel kunnen leren van het perspectief van de patiënt en het invaliderende karakter die epilepsie kan hebben. Door mee te lopen met- en onderwijs te volgen over pre-chirurgische onderzoeken heb ik ook veel kunnen leren over hoe artsen de behandeling aanvliegen en de rol die daarin is weggelegd voor voortschrijdende technologische ontwikkeling. In combinatie met literatuur over epilepsie en behandeluitkomsten heb ik een goed beeld gekregen van dit focusgebied.

Ook de andere ziektebeelden zijn aan de orde gekomen. Naast dat ze allemaal wel minstens eenmaal ter sprake kwamen bij de patiëntendemonstraties, heb ik ook zelf in de kliniek patiënten kunnen zien. Tijdens consulten op de afdelingen en op de Intensive Care kwamen traumata, bewustzijns-stoornissen, slaapstoornissen, cerebrovasculaire ziekten en liquorcirculatiestoornissen allemaal aan de orde. Neuromusculaire aandoeningen heb ik nog iets meer mee kunnen doen door mee te lopen

met de NMZ-artsen en met hen EMGs uit te voeren. Ook hier heb ik inzicht kunnen krijgen in de rol die technologische ontwikkeling kan spelen in bijvoorbeeld de behandeling en diagnose van motore-neuronziekten zoals ALS. Al met al heb ik een breder beeld ontwikkeld van de gehele neurofysiologie.

In bredere zin heb ik mij kunnen bekwamen in het uitvoeren van een anamnese, door bijvoorbeeld patiënten op te nemen alvorens een klinisch onderzoek. Het klinisch redeneren heb ik kunnen trainen in de wekelijkse patiëntendemonstraties, werkgroep-meetings, patiëntenbesprekingen, overdrachten, alsook bij het SUMMA onderwijs over anamnese.

Ik heb mij kunnen bekwamen in (neurologisch) lichamelijk onderzoek, kort neuropsychologisch onderzoek en EEG. Dat laatste met name dankzij het wekelijkse onderwijsmomenten van Frans (medisch begeleider), waarbij ik elke week enkele EEGs voorbereidde en deze ook presenteerde wanneer daar een kans voor was. Daardoor heb ik inmiddels een niveau vergelijkbaar met een AIOS neurologie, als het op EEGs lezen aankomt. Daarnaast heb ik veel meegedraaid in de IEMU bij grid-implantaties en stereo-EEG opnames, waardoor ik goed op de hoogte ben van hoe een epileptische focus wordt gelokaliseerd en functionele corticale gebieden worden afgebakend. In de regionale en landelijke werkgroepen heb ik geleerd hoe behandelplannen in samenwerking met andere centra worden opgesteld en hoe medische professionals zich onderling verhouden in een dergelijke situatie.

Vanuit mijn opdracht heb ik mij met name beziggehouden met electrocorticografie (ECoG) bij grid-implantaties. Daarbij heb ik laborantendiensten gedraaid op IEMU, waar ik samen met een verpleegkundige verantwoordelijk was voor het in de gaten houden van de patient, voornamelijk wanneer deze een aanval krijgt. Hierbij kon ik ook alvast vooruit lopen op de beoordeling door de behandelend neuroloog of TG door alvast markers te zeten in de opname. Al deze ervaring heeft me een aardig gevoel gegeven voor het ECoG.

In relatie tot mijn interesse in de gezondheidswetenschap heb ik ook een beter beeld ontwikkeld over de rol van de neurologie in de volksgezondheid. Vooral de wekelijkse klinische patiënten-demonstraties hebben mij laten zien hoe *evidence-based medicine* te werk gaat in de neurologie. De toenemende rol van genetica, en de valkuilen die daarbij komen kijken staan mij het meest bij. Als voorbeeld wil ik de impact op de levenskwaliteit van familieleden van patiënten met een erfelijke aandoening noemen: door familieleden te screenen voor een dergelijke aandoening kan hun levenskwaliteit achteruitgaan, zelfs als ze geen drager zijn van het gen; door iets dat lijkt op schuldgevoel. Na deze stage realiseer ik mij nog meer dat bij alle onderzoeken en interventies die we doen in de medische praktijk, we stil moeten staan bij de effecten ervan. Soms zijn deze effecten ook minder opvallend en niet zo voor de hand liggend.

Door het frame van een academisch ziekenhuis heb ik wellicht meer bijzondere casussen meegemaakt dan dat ik in aanraking ben gekomen met de meest voorkomende casuïstiek, maar dankzij de vele onderwijsmomenten waarbij ook specialisten uit perifere ziekenhuizen aan bod kwamen, heb ik toch aan aardig beeld gekregen van het hele neurologische werkveld.

Kennis anatomie, fysiologie, pathologie

Na een klein jaar hier in de kliniek, alsook met mijn nodige ervaring en kennis van daarvoor, kan ik inmiddels stellen dat ik over de nodige bagage beschik aan kennis van anatomie, fysiologie en pathologie van het centrale zenuwstelsel. Ook heb ik nu een stuk meer kennis over het perifere zenuwstelsel dan ik voorafgaand aan de stage had verwacht.

Mijn kennis over de anatomie en embryologie heb ik wederom onderwezen tijdens de hersendissectie-practica in Nijmegen. Dankzij onderwijsactiviteiten, zoals de IEMU-cursus heb ik ook meer kunnen leren over de pathofysiologie van epilepsie. De vele hersenoperaties die ik heb bijgewoond hebben mijn kennis verder uitgediept en de theorie voorzien van een praktische bekrachtiging. Ook de wekelijkse klinische patiëntendemonstratie heeft mij een breder inzicht in de pathologie gegeven.

Mijn kennis over de pathofysiologie van epilepsie, over epilepsiechirurgie en over corticale stimulatie heb ik ook kunnen delen buiten het ziekenhuis. Zo heb ik met veel plezier een lekenpubliek op vermakelijke wijze een inkijk gegeven in mijn stage-activiteiten tijdens de *Science Slam* in Wageningen.

Onderzoeksvaardigheden

Een belangrijke pijler aan het begin van mijn stage was het opvijzelen van mijn onderzoeks-competenties. Ik had mijzelf tot doel gesteld om mij te bekwamen in het uitvoeren van klinisch-wetenschappelijk onderzoek, mede om mij ook te oriënteren op een eventueel vervolg in het onderzoeksveld.

Veel zaken hebben bijgedragen aan mijn persoonlijke ‘gereedschapskist’ voor klinisch-wetenschappelijk onderzoek. Een voorname component daarvan is de cursus Basic Course for Clinical Investigators (BROK) die ik heb gevolgd, waar ik met de nodige energie en moeite toch een mooi resultaat voor heb gehaald. Met dit certificaat op zak ben ik aantoonbaar bevoegd om wetenschappelijk onderzoek in de kliniek uit te voeren en mij door de jungle van regelgeving te slaan.

In het werk aan mijn opdracht heb ik steeds getracht het wetenschappelijke karakter te benadrukken. Door de opdracht bijvoorbeeld aan te vliegen met een diepgaande literature review, heb ik een goede basis gelegd voor onderbouwde keuzes later op de weg. Hoewel het enerzijds spijtig is dat in de loop van mijn stage een vergelijkbare review is gepubliceerd vanuit een ander centrum, is het anderzijds fijn dat die publicatie niet tot nieuwe inzichten leidde en de bevindingen grotendeels overeenkwamen. Een ander voorbeeld is het gebruiken van een nieuwe databasestructuur voor mijn onderzoek. Deze database is gedurende mijn stage is ingericht door een aantal onderzoekers, waaronder mijn directe begeleider. Door als één van de eersten deze database-structuur te gebruiken in mijn workflow heb ik de ontwikkeling ervan kunnen aanzwengelen en er zelf aan kunnen bijdragen. De data die ik heb geannoteerd en schoongemaakt kan daardoor ook in de toekomst verder worden gebruikt voor meer retrospectief onderzoek, iets dat mijns inziens past bij een moderne vorm van onderzoek.

Verder waren er vele momenten waar ik goed kon proeven van de wereld van de wetenschap. Uiteraard hadden we onze wekelijkse lab-meetings, waar ikzelf ook een aantal keer een voordracht heb gehouden om met andere onderzoekers te sparren over mijn project. Daarnaast heb ik veel plezier beleefd aan de *Journal Clubs* van de epilepsiegroep, alsook een enkele keer met de

neurochirurgen. Ik heb vooral genoten van het kritisch kijken naar gebruikte methodologie in hoog-aangeschreven publicaties, waarmee we gezamenlijk onze onderzoeksvaardigeheden bijscherpten.

Ook buiten het ziekenhuis waren er zeker noemenswaardige activiteiten. Zo heb ik kunnen deelnemen aan lezingen over machine learning aan de Universiteit Utrecht, en de SWO midwinter meeting van de Nederlandse Liga tegen Epilepsie. Daarnaast heb ik een abstract ingediend voor het MHSDE congres in Lausanne in september, waar ik een poster over mijn onderzoek zal presenteren.

Ik had gehoopt om mee te kunnen draaien met het REC2Stim project van Dorien (directe begeleider). Helaas is dit (hoog-risico) onderzoek tegen enkele hobbels aangelopen waardoor het pas in september van start gaat. Wel heb ik door het aanschouwen van de uitdagingen waar Dorien zich doorheen heeft weten te slaan een goed beeld gekregen van het traject dat een dergelijk wetenschappelijk onderzoek moet doorlopen. Door op te treden als onafhankelijke software-tester heb ik ook een bijdrage kunnen leveren aan de uiteindelijke goedkeuring.

Uiteindelijk kan ik nog net aan het einde van mijn stage meehelpen in de daadwerkelijke implantatie van een corticale neurostimulator, en kan ik dan meteen (hopelijk) ook het resultaat van mijn project valideren in de kliniek! Alles bij elkaar genomen, durf ik te stellen dat ik een aardig beeld heb kunnen vormen van het werkterrein van een klinisch onderzoeker, en ik in principe klaar ben voor een vervolg in het onderzoek.

Zelfsturing

Een grote uitdaging bleek wederom om de regie te hebben in de eigen opdracht. De vaardigheden uit de M2, om vooral wel concrete doelen voor mezelf te stellen, heb ik op verschillende momenten goed ingezet. Ook bleek het soms nog best een uitdaging, vooral wanneer ik een eenzijdige taak had en het niet nodig leek om dat verder op te delen. Wat daarbij goed hielp was het hebben van een richtpunt in de week, waarop ik mijn doelen kon afstemmen. Hiervoor gebruikte ik het wekelijkse sparren met Dorien, en later ook de wekelijkse lab-meetings. Ook steun aan het thuisfront heeft mij geholpen om wat structuur aan te brengen in mijn opdracht.

Een ander aspect wat er nog bij komt kijken is mijn neiging tot perfectionisme, waardoor ik soms wat lang blijf hangen, omdat ik alles tot op de puntjes uitgewerkt wil hebben. Ik heb geleerd dat dit niet persé slecht is, maar dat het wel als risico meebrengt dat ik daardoor kansen mis om zaken eerder te overleggen en inbreng van anderen hierin mee te nemen. Achteraf ben ik tevreden over de perioden waarin ik inderdaad volgens mijn eigen planning heb gewerkt. Vooral in de tweede helft van de stage heb ik daar de vruchten van geplukt. Deze stage heeft me wederom laten zien hoe ik ervoor kan zorgen dat ik mijzelf effectief aanstuur, en wat ik daarvoor nodig heb. Ik ga daarom met vertrouwen een volgende stap tegemoet.

Bijlage: Abstract en poster MHSDE congres Lausanne, september 2019

Wished type of presentation: Poster

Topic: Seizure detection

Seizure onset detection for responsive stimulation in the sensorimotor cortex

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Background: In refractory epilepsy patients, large parts of the pericentral gyri are considered inoperable without permanent functional deficits, due to their key role in sensorimotor processing. Responsive cortical electrical stimulation (CES) may be a promising alternative to surgery [1] due to presumed closed-loop early seizure suppression. Improved approaches for specific and fast seizure detection, validated on central lobe epilepsy (CLE) patients, are required for the development of a next generation of implantable responsive CES devices. This study aims to employ a combination of machine learning methods, which have demonstrated sensitive and specific real-time classification of the ictal and non-ictal electrocorticogram (ECoG), and compare performance of the combined algorithm with algorithms used in existing responsive CES devices.
Materials & Methods: Recordings of ten CLE patients, who presented at least three seizures with similar onset characteristics during invasive presurgical evaluation were used. Six bipolar ECoG channels were selected for each patient to represent cortical areas inside and outside the clinically identified seizure onset zone. A patient-specific Random Forest (RF) classifier was trained using a 138-dimensional feature space, consisting of cross-correlation features and a set of per-channel time and frequency domain features. For every patient, performances were evaluated based on early detection sensitivity using leave-one-out cross-validation, and on false detection rate on a 24h test set.
Results and Conclusion: On our data, the algorithm demonstrates improved performance as compared to existing responsive CES device algorithms. The used feature set and patient-specific RF classifier may be employed to achieve closed-loop suppression in future responsive CES implants for CLE treatment.

1. Vassileva, A., van Blooijs, D., et al. Neocortical electrical stimulation for epilepsy: Closed-loop versus open-loop. Epilepsy Res. 141, 95–101 (2018)

Seizure onset detection for responsive stimulation in the sensorimotor cortex

Brain Center Rudolf Magnus
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Background

- In refractory epilepsy, the central lobe is considered largely inoperable
- Responsive cortical electrical stimulation may be an alternative to surgery[1]
- Improved early seizure detection approaches are required for the next generation of implantable stimulators

Aim

Employ a combination of pre-existing machine learning approaches for real-time classification of the ictal and non-ictal electrocorticogram (ECoG), and validate the patient-specific algorithm on retrospective recordings

Methods

- Ten central lobe epilepsy patients with intracranial grid recordings
- Six bipolar channels for each patient, based on seizure onset (SO) involvement:
  - 2x SO-SO
  - 2x NSO-NSO
  - 2x SO-NSO
- 1s epochs, 138 features:
  - 16 time and frequency domain features, per channel
  - 42 global time and frequency cross-correlation features
- Patient-specific Random Forrest (RF) classifier (100 trees), trained on interictal and early ictal (0-20s) epochs from ≥3 seizures

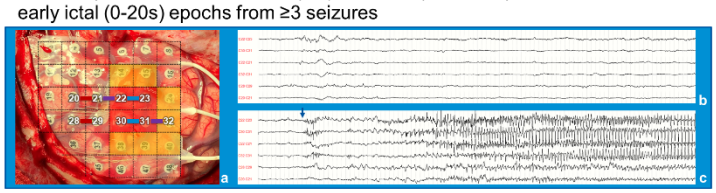

Figure 1 | **(a)** Example of grid implantation and channel selection for RESP0733; **blue**: SO-SO, **red**: NSO-NSO, **purple**: SO-NSO channels. **(b)** Inter-ictal ECoG and **(c)** ictal onset (20s) in selected bipolar channels; **arrow** indicates electrographic seizure onset.

Analysis and interpretation

- Test interictal vs. ictal features for all patients
- Rank features using the absolute value of the standardised U-statistic
- Early (<10s) sensitivity and false detection rate (FDR) based on seizure-level leave-one-out cross-validation
- Additional FDR based on 24-h held-out interictal data for each patient
- Line-length based thresholding algorithm similar to *Neuropace RNS*[2] for comparison

Results

Top feature types:

- *Line-length, fluctuation index*
- *Gamma power, Beta power, Power ratio*
- *Frequency bin cross-correlation, eigenvalue, time-series cross-correlation*
- *Variance / mean absolute deviation*

Table 1 | Number of included seizures, discriminating feature types, and algorithm performance per patient.

Patient No.	Seizures	Top discriminating feature types	Full feature set + Random Forest Classifier				Reference algorithm			
			Sens. (<10s)	FDR_{cv} (/h)	FDR_{test} (/h)	Median delay (s, min-max)	Sens. (<10s)	FDR_{cv} (/h)	FDR_{test} (/h)	Median delay (s, min-max)
295	14	*Line-length, gamma power, eigenvalue freq. cross-correlation, freq. cross-correlation, power ratio*	0.92	2.1	1.8	7 (3-18)	0.89	4.31	7.15	8 (4-17)
733	3	*Line-length, fluctuation index, variance, MAD*	1.00	0.30	0.40	4 (2-8)	0.88	3.82	4.21	6 (2-16)
545	4	*MAD, variance, freq. cross-correlation, eigenvalue freq. cross-correlation, time-series cross-correlation, power ratio*	1.00	0.26	0.34	2 (1-6)	0.25	4.1	3.21	11 (4-18)
529	4	*Line-length, gamma power, beta power, fluctuation index, variance, MAD*	1.00	0.09	0.38	1 (1-3)	1.00	2.23	5.21	1 (1-3)
621	20	*Line-length, power ratio, gamma power, fluctuation index, variance*	1.00	3.01	2.53	5 (1-8)	.83	2.11	3.66	7 (2-12)
677	7	*Fluctuation index, power ratio, freq. cross-correlation, MAD, variance, eigenvalue freq. cross-correlation*	0.93	1.83	2.18	7 (4-15)	.88	3.32	5.21	9 (4-15)
561	10	*Line-length, freq. cross-correlation, power ratio, eigenvalue frequency cross-correlation, gamma power*	1.00	4.01	5.21	3 (2-6)	.94	4.32	9.31	4 (2-11)
608	6	*Line-length, eigenvalue freq. cross-correlation, power ratio gamma power, fluctuation index, beta power*	1.00	1.32	1.12	3 (1-7)	0.73	1.29	2.5	6 (2-13)
294	10	*Line-length, gamma power, beta power, fluctuation index, eigenvalue freq. cross-correlation*	1.00	0.69	0.23	3 (1-8)	0.83	0.71	0.81	5 (1-11)
699	20	*Line-length, power ratio, gamma power, fluctuation index, variance*	.95	0.93	1.05	4 (2-11)	0.90	1.35	3.03	4 (3-12)
		Mean:	**0.98**	**1.45**	**1.53**	**3.9**	**0.813**	**2.76**	**4.43**	**6.1**

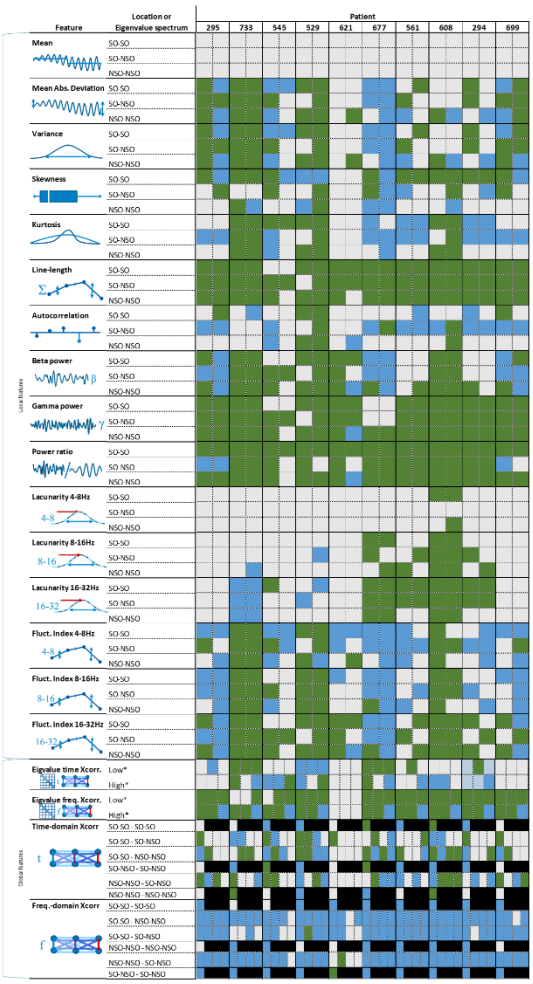

Figure 2 | Overview of significant (P < 0.01/138) changes in feature levels. **Green** represents a significant increase of the feature, blue a significant decrease of the feature value, grey represents no significant change. The 16 **local feature** types are extracted from six bipolar channels for each patient. Local feature channels are grouped in rows by their location's involvement in seizure onset (SO-SO, NSO-NSO, NSO-SO). For **global features**, the eigenvalues are in increasing order (*), with the lower three and higher three shown in two rows. Cross-correlations are grouped by the involvement of each of the correlated channels in seizure onset

Discussion & outlook

- *Line-length, power spectrum features,* and *cross-correlation* features are a useful basis for early seizure detection.
- RF classifier yields improved performance compared to the reference algorithm.
- The used feature set and patient-specific RF classifier may be employed to achieve closed-loop suppression in future responsive cortical electrical stimulation implants
- Further steps from algorithm development to implementation in hardware are being considered
- Used datasets can be expanded upon to create benchmarking set for detecting seizure onset in sensorimotor epilepsy

1. Vassileva, A., van Blooijs, D., *et al.* Epilepsy Res. 2018 | 2. Manzouri, F. *et al.* Front. Syst. Neurosci. 2018