Application of Machine Learning to Enhance the Diagnostic Utility of Interictal High Frequency Oscillations in Drug-resistant Epilepsy

Stefan Sumsky

University of Connecticut - Storrs, stefan.sumsky@uconn.edu

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Application of Machine Learning to Enhance the Diagnostic Utility of Interictal High Frequency Oscillations in Drug-resistant Epilepsy

Stefan Louis Sumsky, PhD
University of Connecticut, 2019

There is a need for novel biomarkers to aid in the clinical treatment of epilepsy and improve the understanding of seizure generation and the seizure onset zone (SOZ). High frequency oscillations (HFO) are a promising biomarker with the potential to fill this role, but early efforts to apply them have fallen short of clinical quality tools and validity and application of their association with seizure have not been fully explored. This study will advance the understanding and application of HFO to the clinical setting in three ways. First, the relevance of HFO to SOZ and their utility for SOZ localization will be determined practically by implementation of an automated method for SOZ localization using intracranial EEG. A novel feature of HFO will be used to train a machine learning system that can accurately identify the SOZ in a patient and patient state independent way with as little 30 minutes of recording. Second, the temporal evolution of HFO occurrence will be characterized using point process modeling and differences in motif manifestation of HFO will be investigated in areas of seizure generation and across epilepsy etiologies to open the door to epilepsy subtype studies using HFO. Finally, to expand the applicability of HFO in both clinical and research settings, a system for the automated detection of HFO from scalp EEG, rather than intracranial, will be developed, using methods of feature and waveform clustering to overcome challenges in noninvasive identification of these events. Together, these approaches will result in the creation of a tool for clinical application of HFO in SOZ localization, provide insights into HFO occurrence and their link to different etiologies of epilepsy, and lay a foundation for new applications of HFO in the previously unutilized area of noninvasive HFO.
Application of Machine Learning to Enhance the Diagnostic Utility of Interictal High Frequency Oscillations in Drug-resistant Epilepsy

Stefan Louis Sumsky

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Doctor of Philosophy Dissertation

Application of Machine Learning to Enhance the Diagnostic Utility of Interictal High Frequency Oscillations in Drug-resistant Epilepsy

Presented by
Stefan Louis Sumsky, B.S.

Major Advisor ____________________________________________________________
Sabato Santaniello

Associate Advisor _________________________________________________________
Monty Escabi

Associate Advisor _________________________________________________________
John Greenfield

Associate Advisor _________________________________________________________
Ian Stevenson

University of Connecticut
2019
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Chapter 1: Introduction

1.1 Overview

Epilepsy is a disease of repeated, uncontrolled seizures occurring in .5-1% of the global population and affecting an estimated 70,000,000 people worldwide (Singh and Trevick 2016). Individuals with epilepsy suffer significant disruptions to their daily lives, ranging from limiting activities and environments out of fear of a seizure occurring to legal restrictions on their ability to drive a car or operate machinery. Less immediately obvious, but arguably worse are the long-term effects of recurrent seizures on brain health and the comorbid diseases associated with frequent or prolonged uncontrolled seizures. For many patients, antiepileptic drugs (AED), such as levetiracetam, carbamazepine, and valproate, provide sufficient control of their condition and allows them to live a relatively healthy and normal life, though sometimes impaired by the noticeable side effects of powerful AEDs. However, for roughly 35% of patients, medication does not provide seizure control (Shorvon and Goodridge 2013; Kwan and Brodie 2000), even after extended periods on a variety of combinations of AEDs. In these cases of drug-resistant epilepsy (DRE), the current gold standard of treatment is a surgical resection of the seizure onset zone (SOZ), i.e., part of the brain assessed by board-certified clinical epileptologists to be the source of seizure activity (Sheng et al. 2018; Rosenow and Lüders 2001). This a risky, expensive, and time-consuming process requiring multiple surgeries and weeks in the hospital. First, patients are admitted to the hospital and taken off their AEDs to allow seizures to occur during video-EEG recording. Patients are monitored with scalp EEG to identify a possible general area of seizure origination. MRI studies are conducted to identify local brain abnormalities, lesions, and dysplasias that could be linked to seizure onset. Once a probable SOZ
has been identified, the patient undergoes surgical implantation of multiple intracranial EEG (iEEG) electrodes to precisely monitor brain electrical activity in the area of interest. After implantation surgery, the patient spends days in the hospital under video surveillance, recording iEEG for a team of epileptologists to analyze, mostly by hand, to determine the SOZ and begin surgical planning. After the clinically-determined SOZ (CD-SOZ) has been identified, another brain surgery is performed to resect the identified tissue, usually a volume ranging from 3-4 square centimeters to an entire lobe of the brain, with correspondingly severe neurological side effects (Rosenow and Lüders 2001). The workflow and timeline for this process is described in Figure 1.1.

**Figure 1.1 - Epilepsy Surgery Workflow**

Determining whether or not a surgery was successful is only possible after the fact as part of the postsurgical assessment. Given the significant personal, physical, and financial toll exacted by these procedures, it is critical that the best possible result is achieved on the first attempt, and in such a way that minimizes the amount of time the patient must spend in the hospital. Patients can only benefit from these surgeries if the SOZ is well-localized and can be safely removed. Part of the reason this is so difficult is that the mechanism of seizure generation
remains poorly understood, and, thus, a safe and accurate method of localization remains elusive. The pursuit of better treatments and outcomes is therefore tied to an improved understanding of the seizure generation and the biomarkers that identify the area of the brain generating seizures.

There is no established electrophysiological criteria to identify the SOZ consistently. In the current clinical setting, SOZ identification is frequently dependent on manually marking the EEG channels in which seizure onset is first present and combining this information with additional multimodal markers of brain abnormality. This method is dependent on the occurrence of multiple seizure events while recording is taking place and requires a significant amount of both patient and clinical time to produce middling results. Development of biomarker that does not depend on the ictal period would significantly ease clinical burden during surgical planning and possibly provide insight into the origin of seizure generation. One promising candidate for such a biomarker is high frequency oscillations (HFO), pathological electrophysical events detectable in EEG with a spectral frequency between 80-500 Hz. While the literature shows good evidence for a relationship between HFO and the SOZ, both this relationship and the events themselves remain poorly understood and attempts to apply them to problems of seizure prediction and SOZ identification have produced inconsistent results with poor clinical utility. More work and new tools are needed to determine and realize the diagnostic potential of HFO. The goal of this proposal is to develop machine learning tools to use HFO more effectively in a clinician-accessible way to improve patient outcomes, while enhancing understanding of HFO themselves, and expand HFO utility from strictly iEEG settings to scalp EEG.
1.2 Statement of Purpose

There is a need for novel biomarkers to aid in the clinical treatment of epilepsy and improve the understanding of seizure generation and the seizure onset zone. HFO are a promising biomarker with the potential to fill this role, but early efforts to apply them have fallen short of clinical quality tools and the validity of their association with seizures has not been fully explored. Current applications of HFO fail to provide a robust and useful implementation for clinical applications due to inconsistent results and limitations in generalizability. Furthermore, many attempts to use HFO in this manner fail to take into account the characteristics of the events beyond simple measures like rate of occurrence. Broader application of HFO is hindered by current limitations in their detection and analysis to intracranial EEG recordings, limiting the population of patients and epilepsy etiologies available from which to collect data and draw conclusions. While improvements in clinical applications of HFO are possible using intracranial recordings, analyses requiring a larger population of events will depend on noninvasive methods for HFO detection and identification. Without additional advances in both understanding and application of these pathological events, there is insufficient basis to create tools the field needs to advance, and the potential benefits to patients and clinicians remain unrealized.

To advance the understanding and application of HFO to the clinical setting, this dissertation will take a 3 stage approach. First, the relevance of HFO to SOZ and their utility for SOZ localization will be determined practically by implementation of an automated method for SOZ localization. Second, work will be performed to characterize the occurrence of HFO and investigate differences in manifestation of HFO in areas of seizure generation and across epilepsy etiologies to open the door to epilepsy subtype investigations using HFO. Finally, the possibility of successful and accurate detection of SOZ from scalp EEG will be determined and characterization of the resulting events will be performed.
1.3 Specific Aims

With these problems in mind, this proposal targets 3 general aims, each aimed at providing both practical and theoretical advances.

**Research Aim 1: Determine whether HFO’s can be used as a reliable biomarker for the localization of the SOZ in patients.**

Novel nonlinear features of HFO from intracranial EEG recordings and their correlation with the SOZ will be explored. Moreover, machine learning and the investigated features will be used to develop a patient-independent algorithm for the precise localization of the SOZ using short-term (i.e., less than one-hour-long) intracranial EEG.

**Research Aim 2: Characterize the temporal evolution of the HFO’s as the brain transitions through wakefulness and sleep stages over multiple days.**

It is hypothesized that epileptogenic HFO’s follow distinct multi-day patterns that are specific to the SOZ and related to the epilepsy etiology. However, the transient nature of these patterns has prevented their detection thus far. A computational framework based on point process modeling and a unique cohort of multi-day intracranial EEG recordings will be used to test this hypothesis and to assess the predictive power of the HFO’s temporal pattern in SOZ localization.

**Research Aim 3: Determine the detectability of epileptogenic HFO’s in scalp EEG recordings and understand the relationship between scalp HFO’s and intracranial HFO’s.**

Scalp HFOs have been investigated in the past few years as a noninvasive biomarker of epileptogenic activity but detection methods and analyses are lacking. In this aim, EEG data from a unique cohort of young epileptic patients from the CT Children Medical Center will be used to develop machine learning tools for the unsupervised detection of
scalp HFOs. Characterization of the temporal and spectral properties of scalp HFO’s in different brain states will also be performed.

1.3.1 SOZ Localization by HFO
The primary purpose of aim one is to determine through practical means (i.e. implemented proof of concept) the viability of HFO as a diagnostic biomarker for the localization of the seizure onset zone. While theoretical proof of whether or not HFO can be used clinically have a place, a tool developed and tested for this purpose on a varied and challenging dataset and validated with high accuracy in a robust framework can accomplish this goal while more rapidly advancing the ultimate goal of full and useful clinical implementation. To this end, such a tool will be developed, compared to the current state of the art, and tested as subassemblies to determine the relative contributions of each component of the system.

The majority of current approaches to automated localization still rely on the raw HFO rate as a feature set. To verify that the poor performance of current systems is due to the choice of feature rather than a limited computational approach, a baseline system based on rate will first be designed using straightforward but powerful machine learning tools and the results of this system will be quantified.

A new system of rational feature transformation based on the current body of literature about HFO (see Chapter 2) will be used to improve the diagnostic utility of HFO above this baseline and provide the feature set for a SOZ localization system with a minimum performance standard of at least 90% accuracy, while use the same machine learning tools applied in the baseline system.

Once the system has been optimized in terms of amount of training data, feature selection, and machine learning details, the machine leaning tool used in the final solution will
be replaced with a less powerful alternative to determine the extent to which the system’s success is dependent on the machine learning tool in question rather than the novel feature transformation.

Together, these steps will show that HFO can be adapted to overcome current challenges to their diagnostic utility, that the resulting tool can potentially meet standards for clinical application, and, by showing how the feature transformation improves diagnostic utility, augment understanding of the relationship of HFO to SOZ.

1.3.2 Temporal Evolution of HFO

The primary goal of aim two is characterization of the temporal pattern of HFO, with the secondary goal of investigating the relationship of variations in this pattern to both the SOZ and to epilepsy occurring in different regions of the brain. The temporal pattern is of interest both as a potential marker of epileptogenicity and as a window into the underlying pathology of seizure generation and circuitry at the macro level.

Aside from variations in HFO rate, no pattern in the HFO occurrence has yet been described in the literature. This suggests that the pattern (if one exists) is either very subtle or highly transient and large amounts of data and sensitive identifications methods are needed to detect it. This project will use history-dependent point processes models, fitted on multiple days of iEEG recording with detected HFO, to characterize the pattern in individual patients and aggregate to the population level. Variations in pattern inside and outside the SOZ and between patients with different SOZ locations will be analyzed and theoretical interpretations of these differences will be explored.
1.3.3 Scalp HFO

Aim three diverges from the previous work on intracranial HFO and attempts to develop a consistent and useful detector of scalp HFO that overcomes previous detectors’ high false positive rate by multifaceted characterization of spectral and waveform characteristics of the putative HFO events and clustering-based elimination of artifacts and false positives. In collaboration with clinicians at CCMC, the accuracy of the detection algorithm will be assessed. Additionally, the final set of detected scalp HFO will be analyzed and insights into scalp HFO characteristics will be reported.

1.4 Summary

The proposed research plan delivers novel HFO-based biomarkers and computer tools to assist epileptologists with the planning of the epilepsy surgery (Aim 1). Highly precise SOZ localization methods are expected to prove the utility of HFO as a predictor of the SOZ and enhance the outcome of the epilepsy surgery. This project also establishes a link between the temporal evolution of HFO events in the SOZ and the correspondent epilepsy diagnosis (Aim 2), which is important to understand the origins and pathophysiology of the epileptogenic HFO’s. Finally, it will be determined whether HFO’s are detectable noninvasively and how well these events correlate with the epileptogenic activity (Aim 3). This is of critical importance to reduce the need for invasive iEEG recordings as part of epilepsy surgeries as well as to facilitate the development of novel noninvasive methods for the analysis of the epileptic brain. Taken as a whole, this dissertation confirms and demonstrates the diagnostic utility of HFO, provides characterization of a previously undetected pattern of HFO occurrence in intracranial recordings, and lays a practical groundwork for generalization and broader application of these findings in a noninvasive setting.
Chapter 2: Literature Review

2.1 High-frequency Oscillations

High-frequency oscillations (HFO) are pathological EEG events occurring between 80 and 500 Hz with at least 3 zero-crossing oscillations (J. Jacobs et al. 2012). HFO between 80 and 250 Hz are classified as ripples, while those from 250-500 Hz are classified as fast ripples (Wang et al. 2013). This proposal will examine the relationship between both intracranial EEG and scalp EEG HFO’s and the SOZ to assess their utility.

2.1.1 Intracranial EEG

The first interictal “HFO” events were identified by Bragin and Engel in microelectrode arrays in 1999 in animal epilepsy models (Bragin et al. 1999), and later generalized their work to the human hippocampus (Bragin, Engel, Wilson, Vizentin, et al. 1999; Bragin, Engel, Wilson, Fried, et al. 1999). Early detected events were noteworthy for their similarity to CA1 ripple oscillations known to originate from synchronously discharging interneurons generating fast inhibitory postsynaptic potentials between 80-200 Hz (Ylinen et al. 1995; Buzsaki et al. 1992). Later events with higher frequency spectral characteristics, termed ‘fast ripples’, were detected and hypothesized arise from synchronous bursts from excitatory principal neurons (Bragin, Engel, Wilson, Fried, et al. 1999). Larger scale studies showed a strong association with the SOZ, with consistent ipsilateral association between fast ripple rates and location of SOZ, but a less consistent association with ripples (Staba et al. 2002; 2004). Rates of both ripples and fast ripples were elevated during non-REM sleep, partially consistent with higher incidence of seizures occurring out of sleep (Staba et al. 2004). This result is confounded however by the known increase in similar, non-pathological ripple events during sleep. Determination of the origin of the events and discrimination between normal and pathological ripples remains a
challenge. Voltage-depth studies of HFO have shown that fast ripples are more tightly localized to a point of origin than ripples, indicating that ripple originate from a broader area of brain network (Bragin, Engel, Wilson, Fried, et al. 1999). The troughs of these ripple HFO events have been shown to be in sync with the linked firing of multiple inhibitory interneurons (Jiang et al. 2019).

However, more complete exploration of these phenomena requires either a larger pool of events from human subjects or continuing research in animal models. Kainic acid and pilocarpine rat models of epilepsy have been used to investigate features of HFO. These studies have the benefit of targeted SOZ creation, eliminating the potential uncertainty of SOZ identification by clinicians when comparing events inside vs outside the SOZ. These studies confirm results from human microelectrode recordings showing the HFO rates are generally higher in the SOZ (Bragin et al. 2004; Worrell et al. 2008) and that the spectral characteristics of HFO are not sufficient to discriminate pathological and physiological events, particularly in cases where physiological and pathological events overlap (Jr et al. 2009). Other discriminatory factors may be needed. Animal studies do indicate that pathological HFO arise from abnormal bursting of a population of neurons in an apparently spontaneous way (Bragin, Wilson, and Engel 2007; Song et al. 2017). It is hypothesized that temporal pattern analysis may be necessary to distinguish pathological HFO (Schevon et al. 2009).

In 2006, it was shown that iEEG electrodes could successfully pick up HFO activity (Jirsch et al. 2006; Akiyama et al. 2005; Blanco et al. 2010), opening the door to clinical research into the phenomena. Recordings taken during the course of clinical surgical planning could now also be used to investigate HFO. Additionally, this increased interest in these events as clinical biomarkers because they could now be collected for assessment without additional recording
time or techniques. Since then, significant findings linking HFO to the SOZ have emerged. Early results from these studies confirmed prior microelectrode results (Julia Jacobs et al. 2008), enabling partial validation of those early findings in a more clinically applicable model. Furthermore, the expanded types of data available for analysis, finally including regions outside the temporal lobe, showed that HFO can occur anywhere in the brain where an epileptogenic source is present. This important and welcome finding is complicated by the detection with clinical electrodes of HFO events in areas of the brain not associated with the SOZ. This finding presents difficulties for the use of HFO in the clinical setting as a diagnostic or localization tool. This raises the question of whether the epileptogenic zone is larger than previously believed, or if HFO are actually not specific to the SOZ. However, further investigation provides compelling evidence of the association of HFO with SOZ, in spite of these findings. First, it was shown that HFO events were localized to the area of seizure generation, not the location of tissue lesion associated with the cause of the epilepsy (Julia Jacobs, LeVan, et al. 2009), suggesting HFO utility for localization may be more accurate than that enabled by MRI. Second, brain regions showing HFO activity outside the SOZ have been found to be more likely to respond to electrical stimulation with epileptic events (Julia Jacobs et al. 2010), supporting the hypothesis that the epileptogenic zone can extend beyond the SOZ. Third, HFO occurrence has also been found to increase just prior to seizure onset (Khosravani et al. 2009). Furthermore, upon removal from anti-epileptic drugs, patient recordings show a significant increase in the number of HFO (Zijlmans et al. 2009). Other studies have found that HFO rate correlates with disease severity (van Klink et al. 2016) and that propofol, a known antiepileptic, decreases the number of HFO (Zijlmans et al. 2012). Finally, the link between HFO and epileptogenicity is most strongly supported by the growing body of evidence from clinical studies that removal of HFO generating
tissue is the best way to achieve optimal patient outcomes in a surgical setting. One such study showed a link between complete removal of the HFO-generating tissue and a successful surgical outcome (Ochi et al. 2007). Three additional studies have shown a correlation between the proportion of the HFO-generating tissue removed during surgery and the degree of success in the surgery (Akiyama et al. 2011; Julia Jacobs, Zelmann, et al. 2009; Julia Jacobs et al. 2018). The most convincing study to date of HFO and SOZ by Wu and coworkers was a case study involving a two stage surgery (Wu et al. 2010). The first operation failed to remove all the HFO-generating tissue and failed to reduce or stop seizure occurrence. In the second stage of the surgery, the remaining HFO-generating tissue was removed and the patient achieved complete seizure freedom. Together, these findings show that there is a clear and consistent link between SOZ and HFO, meritng further work and efforts to refine these results and apply HFO to the clinical setting.

An important part of determining the viability of HFO as a clinical biomarker is comparison with other possibilities, to ensure that HFO are the best option for the job. While HFO are strong candidate as biomarker for epileptogenicity, epileptic spikes have also been investigated as a biomarker. The link between HFO and spikes, and an assessment of their relative utility is necessary to guide the most appropriate direction for research. The current body of research shows that HFO and spikes occur in 3 types of relation to each other: HFO independent of spikes, HFO occurring on top of spikes and visible in unfiltered EEG, and HFO occurring with spikes but visible only in filtered signal (Julia Jacobs et al. 2008; Urrestarazu et al. 2007). The majority of HFO occur on top of spikes, with 81% of HFO occurring in tandem with spikes, either visible or not. However, despite this association, studies have shown that spikes and HFO most likely have different physiological mechanisms and clinical interpretations,
even when co-occurring (Julia Jacobs et al. 2008). They also respond differently to changes in clinically relevant conditions. While, as mentioned above, HFO rates drop when a patient is given anti-epileptic medication and rise when that treatment is removed, spikes show no change in response to treatment of epilepsy. Additionally, HFO rates do not increase post-ictally (Zijlmans et al., n.d.); spikes do. Conversely, HFO rates have been observed to increase prior to seizure (Zijlmans et al. 2009), which has been interpreted as further evidence of a link between HFO and epileptogenicity. No such increase is observed with spikes. As one might expect from these findings, HFO have been shown to be a better predictor of SOZ than spikes. HFO are more strongly associated with the seizure onset zone than spikes, with a 52% sensitivity for HFO vs 33% for spikes, based on a simple rate threshold (Urrestarazu et al. 2007). This finding alone provides a good basis for the decision to focus efforts on using HFO for clinical applications. In the light of the above findings, it is plausible to suggest that rather than HFO being associated with spikes, it is most useful and accurate to think of spikes as secondarily associated with HFO, especially in terms of relationship to epileptogenicity. HFO, not spikes, should be the area of most intense focus for studies of SOZ and epileptogenicity. Accordingly, this dissertation is focused here.

Given the strong evidence of HFO as the leading biomarker for clinical work in epilepsy, it is understandable that significant work has been undertaken to determine how consistent their link to the SOZ is. Studies have been performed attempting to localize the SOZ using during different sleep stages, during periods of both high and low seizure activity, in medicated and unmedicated states, and during normal clinical procedures (Staba et al. 2004; Bagshaw et al. 2009). These studies confirm previous findings that, at the population level, HFO rates are generally higher in the SOZ than in distant tissue, with higher variability in the regions near the
SOZ (Julia Jacobs, Zelmann, et al. 2009). Despite these promising findings, researchers have so far been unsuccessful in applying HFOs as predictive diagnostic biomarker in the case of individual patients. While the link between HFO and SOZ is clear at the aggregated population level (Urrestarazu et al. 2007), *high interpatient variability in HFO rate currently confounds its use as a generalizable biomarker in a clinical setting*. Likewise, significant variability in HFO rate for a single patient over time creates challenges to the use of HFO biomarkers even in a patient-dependent manner, and further limits the applicability of HFO as a clinical biomarker (Frauscher et al. 2017). Numerous of variation have been revealed by the above studies. The region of the brain in which the SOZ lies can greatly impact baseline HFO rates, with temporal lobe epilepsies showing higher HFO rates than neocortical areas (Julia Jacobs, Zelmann, et al. 2009). Differences in underlying pathology, type of electrode used, patient state, time of day, sleep phase, and more have all been shown to alter HFO rate both in and out of the SOZ. Because of this, existing attempts at clinical implementation face a serious problem in determining if an area of the brain is epileptogenic in any individual patient specific case. A rate indicating the SOZ in one patient may be outside the SOZ in another. Thus far, all attempts to implement an automated localization method have not met the criteria for application in a clinical setting. These attempts include analysis of HFO time-frequency content (Kobayashi et al. 2010; Malinowska et al. 2015; Elahian et al. 2017; Pearce et al. 2013), and limiting focus to fast ripples (Staba et al. 2004; Akiyama et al. 2011), which would require an iEEG sampling rate (>1000Hz) not available at many clinical centers. Novel techniques of analysis are necessary to overcome these obstacles and enable the practical use of HFO.
2.1.2 Scalp EEG

The work discussed thus far is taken only from studies of intracranial recordings. But many phenomena detectable by intracranial electrodes are also present in some form on scalp EEG. The ability to detect and apply HFO in a non-invasive manner would potentially increase the utility and widespread applicability of HFO as a means to multiple less critical interventions than surgical planning, including assessments of disease progression and early estimation of potential treatment efficacy. Furthermore, a non-invasive option would necessarily allow for reduction or avoidance of risks of intracranial recording. Scalp EEG recordings are widely available, easily collected from a far greater variety of epileptic patients, and create far less risk for the patient. Additionally, the relatively low cost of scalp EEG makes it a more attractive option for new, large scale studies than modalities like MEG. There is strong evidence, both clinical and theoretical, that supports the possibility of successful HFO identification from scalp EEG. The earliest clinical evidence comes from studies of pediatric patients that shows the ability of clinicians to mark HFO events just prior to seizure onset in association with epileptic spasms. Additional investigations of non-invasive HFO detection in adults support the possibility of meaningful detection of HFO prior to seizure from scalp EEG recordings (Andrade-Valenca et al. 2011; van Klink et al. 2016). HFO events have also been marked interictally, in both children and adults(Kobayashi et al. 2004; Inoue et al. 2008). The majority of these markings occurred during slow wave sleep. For this reason, it was once suspected that scalp HFOs were not true HFO as detected in intracranial recordings. More recent work has settled the questions in multiple ways. Simulations have shown that it is entirely possible to successfully detect HFO events and high frequency signal from 80-200 Hz successfully (Kobayashi et al. 2010). More practically, and of greatest relevance to the clinical setting, comparison of simultaneous scalp and iEEG recordings have confirmed that detected scalp HFOs
originate from the cortical HFO (Zelmann et al. 2014). Based on this, scalp HFO may represent the next frontier in HFO research and allow for both expansion in the application of existing methods and theories, as well as enabling new applications for HFO in the clinical setting.

Clinical research into the use of scalp HFO is still in the early stages. Not all studies looking to mark scalp HFO have done comparison with SOZ or other factors of clinical interest. Those that have show promising results. All early studies show that hand-marked scalp HFO successfully localize to the affected lobe and hemisphere according to clinical assessment (van Klink et al. 2016; Melani et al. 2013; Zelmann et al. 2014; Pizzo et al. 2016). This is an important first step towards more direct clinical application, as well as support for confidence in the relevance of these events and their relationship to the more established intracranial HFO. But widespread or simple clinical application of these events cannot come from doctors manually marking each individual event from hours of EEG recording. The rapid evolution of this path of research is dependent on the development of automated detection of HFO from scalp EEG. However, automated detectors have yet to produce meaningful results and small sample sizes and significant time investment for manual HFO marking limit the clinical applicability of existing studies (Chu et al. 2017).

Current attempts to develop automated scalp HFO detectors have shown that it is possible to generate a pool of putative HFO events with an automated detector using techniques and features similar to those applied in intracranial EEG. But the challenges to detection from scalp EEG are far greater than intracranial. Because of the high level of signal attenuation by the skull, there is a large drop in amplitude of the signal, particularly at high frequencies, which are of the greatest interest in this application (Zelmann et al. 2014).
The reduction is so severe that HFO become exceedingly difficult to detect against the background, even when the signal is clear. Additionally, scalp electrodes necessarily record from a larger area and blend of sources, making fine localization more difficult. Figure 2.1 clarifies these challenges. To complicate matters, the amount of noise and artifact in scalp EEG is much higher than in intracranial EEG. These problems combine to limit the current success of HFO detectors. The current state of the art suffers from oversensitivity and a very high false positive rate, rendering its clinical usefulness limited. Additionally, the same caveats for the use of HFO recorded from iEEG apply to the application of HFO detected from scalp EEG. While generalizable trends are present in HFO distribution, high variability in both inter- and intra-patient HFO rates current limits their application in a clinical setting (Frauscher et al. 2017). Parallel improvements in both intracranial and scalp HFO research are needed to see widespread application in this area.
Chapter 3: Investigation of the Diagnostic Utility of HFO in Epilepsy

3.1 Introduction

In this chapter, the goals cited in aim one of this dissertation will be addressed. These goals include automated detection of HFOs from intracranial EEG, determination of the diagnostic utility of detected events as rate alone or as a transformed feature, and implementation of a patient-independent system to assist in clinical surgical planning as a proof of concept example.

3.2 Methods

3.2.1 Dataset

Fourteen de-identified patients with drug-resistant epilepsy from the National Institutes of Neurological Disease and Stroke iEEG Portal (https://www.ieeg.org/) were included in this study. Information about the patients’ epilepsy etiology, iEEG recording setup, and signal processing stages are reported in the following sub-sections.

3.2.2 HFO Detection

As noted in the introduction to this dissertation, well-validated HFO detectors for iEEG recordings already exist in the literature. One such detector (Gliske et al. 2016) was implemented with enhancements to provide a pool of HFO events for analysis most consistent with the “gold standard” in the field. For each patient, the detection algorithm begins by taking the common average reference of electrodes in the recording. This is analogous to the average reference montage in scalp EEG and is commonly used when recording iEEG with high numbers of electrodes. After this step, each channel for a given patient is processed independently. Recordings were high pass-filtered above 100 Hz to isolate high frequency components and
divided in to 10-minute epochs to be analyzed separately. Detection was applied in stages. An initial pool of candidate events was marked by identifying recording segments that had a RMS line length 5 SDs greater than normal for the epoch over a duration between 10-150 ms were marked putative HFO. Events less than 10 ms away from each other were merged. Next, all putative HFO with less than 5 peaks with amplitudes 3 SDs greater than baseline and with fewer than 4 zero line-crossings were eliminated. A selection of events were visually inspected to assess detection quality. Events were not separated according to status as “ripples” or “fast-ripples,” as defined in Chapter 2.

3.2.3 Exploratory Assessment of Rate-based Classification and the Limits of HFO Rate as a Predictor of SOZ

It is well established in the field that HFO rate shows a strong, if inconsistent, association with the SOZ. The simplest assessment of the diagnostic utility of HFO would be the implementation of a SOZ classifier using the HFO rate as the feature set. A “current best-practice” approach was applied to a representative subset of the dataset to establish a baseline level of performance to improve on. A trial classifier was developed on 5 Engel Class I post-surgery patients from the iEEG database. Using the HFO rate for each 10 minute detection epoch for each channel as input feature vectors, a linear Support Vector Machine classifier was trained on the data for 4 of the patients, using clinical assessment of SOZ and non-SOZ channels for labels, as described in Chapter 2, and tested on the fifth patient, and repeated in a standard leave-one-out cross validation. Classifier success was assessed by measuring the area under the ROC curve.

Rate-based SVM failed to provide useful classification of SOZ channels in every patient. AUC values for the validation set were .51+-.07, indicating a prediction accuracy at chance levels. Investigation of the specific misclassifications found that classifier was completely unable
to identify SOZ channels, generally labeling nearly all channels as non-SOZ, or in some cases all channels as SOZ. This problem is likely indicative of an issue in hyperplane creation analogous to the thresholding problem discussed in Chapter 2. It was determined that even with powerful machine learning techniques like SVM that difference in HFO rate between SOZ and non-SOZ channels was not significant enough to be useful for clinical applications in an automated or patient-independent way.

3.2.4 Susceptibility Index

Raw HFO rate suffers from 2 primary weaknesses as a machine learning feature. First, poor intra-patient separability between SOZ and non-SOZ channels due to high variability over time and inconsistent baseline rates. Figure 3.1 highlights how, while in some cases, HFO rate is consistently higher in SOZ, this is not the case for all channels and there are many periods where rates are closer or nearly identical. And second, low inter-patient reliability due to large differences in baseline rate between patients, as discussed in Chapter 2.

Figure 3.1 – HFO rate over time in sample channels
A nonlinear data transformation was developed to address these challenges. While raw HFO rates are highly variable across time, it is possible that the channels with the highest rates are largely consistent and that the SOZ is associated with these channels. Therefore, ranking the channels by rate for each epoch, and identifying which channels are consistently highest across multiple epochs, could provide a way to isolate the SOZ. As an added benefit, once the analysis is shifted from raw rates to channel ranking, the differences in baseline rate between patients is eliminated, allowing for better interpatient analysis and the successful pooling of data across patients for machine learning purposes. The tendency of a channel to consistently have the highest rate was termed the Susceptibility Index. Figure 3.2 summarizes the proposed workflow. In brief, HFO events are detected and the HFO rate for each 10 minute window is calculated. For each window, channels are ranked by HFO rate and a nonlinear transformation of this rank is applied to improve separability and a consensus policy is applied to improve stability and

\[ r(t) = \begin{bmatrix} r_1 \\ r_2 \\ \vdots \\ r_n \end{bmatrix} \]

\[ \text{HFO rate (min}^{-1} \text{)} \]

\[ \text{Channel Rank } R(t) = \begin{bmatrix} 5 \\ n - 1 \\ \vdots \\ 3 \end{bmatrix} \]

\[ \text{Susceptibility Index } S(t) = \prod_{h=0}^{2} e^{1-R(t-h)} \]

\[ \text{SVM}\text{ Classifier } + \text{ Consensus} \]

\[ \text{SOZ channels} \]

Figure 3.2 – SOZ localization workflow schematic
consistency, as detailed below. The resulting feature set is then used to train a SVM classifier and produce an SOZ location estimation.

For each iEEG channel and epoch, the HFO rate was defined as the average number of HFO/minute. Denoted with \( N \) the number of iEEG channels in a patient and with \( f_{i,k} \) the HFO rate of channel \( i=1,2,3,\ldots, N \) in epoch \( k=1,2,3,\ldots \), channels were ranked in each epoch based on the HFO rate values, i.e., the higher the rate \( f_{i,k} \) the lower the rank position of channel \( i \) in epoch \( k \). Denoted with \( \mathbf{R}_k = [r_{1,k}, r_{2,k}, \ldots, r_{N,k}]^T \) the vector of rank positions, where \( r_{i,k} \) is the rank of channel \( i \) and \( 1 \leq r_{i,k} \leq N \), \( \mathbf{R}_k \) was used to define the \( N \times 1 \) vector index:

\[
S_i = \exp(1 - \mathbf{R}_k)
\]

whose elements range between 0 and 1 and increase as the rank value decreases. Intuitively, \( S_k \) aims to characterize the level of epileptic susceptibility in each channel in epoch \( k \). Low values of entries in \( S_k \) correspond to discharge patterns with occasional HFO events (i.e., low susceptibility and high rank in \( \mathbf{R}_k \)) while high values correspond to HFO rates that are consistently above the average trend across channels (i.e., high susceptibility and low rank in \( \mathbf{R}_k \)).

3.2.5 Rank-based Classifier Design and Optimization

With a transformed feature capable of compensating for the inherent problems with HFO rate measurements, a machine learning system was developed for automated classification of SOZ channels from iEEG data, with goals of ensuring patient independent and patient-state independent application. For computational efficiency and consistency of comparison with previously attempted HFO rate classifiers, an SVM framework was chosen. The design of the Support Vector Machine (SVM) classifier used in the Rank-based SVM system was optimized offline on a subset of 60 hours of interictal intracranial EEG data (360 epochs) from 10 randomly
chosen patients, i.e., 36 epochs per patient. First, four classes of kernel functions (linear, third and fourth order polynomial, and radial basis functions [RBF]) were tested and, for each class, the SVM classifier was trained on the rank vectors $S^*$ from five randomly chosen patients (i.e., 180 training epochs) and tested on the remaining five patients (i.e., 180 testing epochs). The final class of kernels was chosen by maximizing the AUC value over the testing epochs. The RBF kernels were chosen because the RBF-based SVM classifier resulted in an average AUC value of $0.92 \pm 0.02$ (mean ± S.D.), which was significantly larger than the values for linear ($0.62 \pm 0.01$) and polynomial (third order: $0.84 \pm 0.01$; fourth order: $0.86 \pm 0.01$) kernel functions.

To further compensate for the variability in channel HFO activity over time, a consensus policy was implemented by combining the output of the RBF-based SVM from $n$ consecutive epochs and the policy performance was tested on the testing epochs. The number $n$ of epochs used in the consensus policy was varied between 0 (i.e., no consensus) and 3 (i.e., 40 min) and the optimal value $n^* = 2$ was chosen by maximizing the average values of area under the ROC curve (AUC), specificity, and accuracy, see results in TABLE 3.1.

<table>
<thead>
<tr>
<th>$n$</th>
<th>AUC</th>
<th>Specificity</th>
<th>Sensitivity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.90±0.04</td>
<td>0.86±0.02</td>
<td>0.91±0.02</td>
<td>0.87±0.05</td>
</tr>
<tr>
<td>1</td>
<td>0.91±0.05</td>
<td>0.90±0.03</td>
<td>0.91±0.03</td>
<td>0.90±0.02</td>
</tr>
<tr>
<td>2</td>
<td>0.92±0.03</td>
<td>0.93±0.03</td>
<td>0.90±0.12</td>
<td>0.92±0.03</td>
</tr>
<tr>
<td>3</td>
<td>0.83±0.05</td>
<td>0.97±0.03</td>
<td>0.41±0.07</td>
<td>0.53±0.06</td>
</tr>
</tbody>
</table>

TABLE 3.1 - Performance Values for Different Durations of Consensus Policy (mean±S.D.)
Steps were also taken to optimize the performance of the proposed classifier by varying the hyperparameters $M$ (i.e., number of patients used in each training set) and $W$ (i.e., number of 10-min-long epochs extracted from each patient in the training set and used to train the RBF-based SVM classifier). A grid search was performed, varying $M$ between 1 and 9 patients and $W$ from 6 (i.e., 1 h/patient) to 96 (i.e., 12 h/patient) training epochs. For each combination, the classifier was then tested on the remaining data (testing) and the procedure was repeated $K=8$ times (K-fold cross-validation). Results in Figure 3.3A demonstrate that parameters $M=5$ and $W=24$ were the smallest values that guarantee (i) an average area under the ROC curve greater than 0.90 across the testing and (ii) an improvement from the subsequent value less than 0.05.

![Figure 3.3](image)

**Figure 3.3 – A) Grid Search Optimization of Rank-based Classifier Performance, B) Rank-based Classifier Performance at $W=24$ for Different Numbers of Patients**

Notably, there is a clear threshold, highlighted in Figure 3.3B between 4 and 5 patients in the training set for significant improvement to useful (>0.90 AUC) levels, consistent across cross-validated training sets. This may highlight the underlying variability between patients and represent a minimum level of interpatient training information to capture the variability in the pathology of drug-resistant epilepsy.
Final implementation of the classifier was as follows: A $K$-fold cross-validation procedure was used to implement *Rank-based SVM*. Patients whose post-surgery outcome was successful (i.e., patients who were Class I according to either the ENGEL scale or the ILAE scale) were as the “gold standard” for accurate group labels and used to train and test *Rank-based SVM*. Patients were split in two, non-overlapping groups (i.e., training set and validation set) of $M$ and $8 - M$ patients, respectively, with $M = 5$. For each patient in the training set, the first $W = 24$ consecutive epochs (i.e., 4 h/patient) were selected arbitrarily and the sequence of $M \times W$ index vectors $S_k$ was used to train the SVM (total: 120 epochs). The trained classifier was then applied on the vectors $S_k$ from every epoch of the remaining $8 - M$ successful patients, covering recordings of multiple hours and a variety of patient states. The procedure was repeated $K = 8$ times by substituting one training patient with one validation patient (no repetition) of each repetition, ensuring that each Class I patient was included in at least one training set and every Class I patient was included in a similar number of validation sets. Additionally, patients with partially successful (i.e., Class II or above) or unreported post-surgery outcomes were used to provide further validation of *Rank-based SVM* and investigate the correspondence of predicted channels of non-“gold standard” to those with a high confidence ground truth. The rationale for using these unsuccessful patients is that, in such cases, *Rank-based SVM* is expected to make predictions about the SOZ that significantly differ from the reported evaluations. Accordingly, the RV in these cases was labeled as “true positive” and the analyses done was repeated for the validation sets.

Assessment of the success of the rank-based classifier was supplemented by comparison to two alternative classifier designs. First, an SVM classifier with radial basis kernel trained on the vectors of raw HFO rates $F_i = [f_{i,1}, f_{i,2}, \ldots, f_{i,s}]^T$ instead of the index vectors $S_k$. The same
training and validation patients as described above were used and the same consensus policy with three consecutive epochs was adopted, to confirm that use of the susceptibility index was the cause of improvement in classification accuracy. This alternative classifier also double-checks that the reason for poor performance of the rate-based classifier described in 3.2.3 is the inadequacy of the raw HFO rate as a feature, not a lack of optimization or consensus policy.

Second, the Rank-SVM classifier described above was replaced with a logistic regression-based classifier, i.e., for each epoch \( k \) and channel \( i \), the probability was calculated as:

\[
P_{i,k} = \left[1 + \exp\left(\sum_{j=0}^{i} \beta_j S_{i,j}\right)\right]^{-1},
\]

where \( P_{i,k} \) is the probability of channel \( i \) being inside the SOZ in epoch \( k \), \( S_{i,k} \) is the \( i \)-th element in \( S_k \), and \( \{\beta_j\} \) are coefficients estimated on the training data via maximum likelihood methods. Channel \( i \) was marked as inside the SOZ in epoch \( k \) if \( P_{i,k} > P \) for three epochs, where \( P \) is the optimal threshold estimated on the training data. This method was included to assess the portion of improvement attributable to the type of classifier used. Together, these points of comparison allowed determination of the relative contributions of the various components (transformed feature vs classifier complexity) to the results.

Classifier performance was computed using the Receiver Operator Characteristic curve. To determine the overall performance of each system, the aggregate classification success was computed first. For each decision system (i.e., \textit{Rank-based SVM}, \textit{Rate-based SVM}, or \textit{Rank-based LR}) and validation set, one ROC curve per patient was computed, along with the 95% confidence intervals, and the area under the ROC curve (AUC) and the values of sensitivity (true positive rate [TPR]), precision (positive predictive value [PPV]), and accuracy (ACC) at cutoff point, which is the point maximizing the Youden index, were determined. Results are reported as
mean ± S.D. across patients and validation sets. For each metric (i.e., TPR, PPV, ACC, or AUC) and validation set, a two-way ANOVA test with Tukey’s post-hoc test ($P$-value $P<0.005$) was performed on the classification results. The type of decision system (i.e., Rank-based SVM, Rate-based SVM, or Rank-based LR) and the patients were used as factor groups.

3.2.6 Development and Assessment of Clinically Applicability of Tool for SOZ Localization

Time and patient-state independence are critical for successful clinical application. To this end, it was necessary to determine the extent to which the classifiers’ success changed over the course of the available clinical recording. This will determine the ability of the localization tool to function accurately on minimal amounts of recorded data and be applied in a patient-state independent way, as needed in the clinical setting. The robustness of the SOZ prediction against the onset time of the consecutive epochs used in the consensus policy was assessed for each classifier and patient in the validation sets. A sliding window of three epochs (sliding by one epoch) was considered and, for each window, the classifiers Rank-based SVM, Rate-based SVM, and Rank-based LR were applied. One ROC curve per classifier and window was built and TPR, PPV, ACC, and AUC over consecutive windows were tracked. The number of windows that each classifier performed above chance level was also measured. For each patient, 72 continuous hours (432 epochs) were used and the average values of TPR, PPV, ACC, and AUC across windows were computed across all windows, with a single exception. In one patient (Study_23), only 48 hours were available (288 epochs) and the average values were computed on the available windows. The average values across patients and classifiers were compared via a two-way ANOVA test with Tukey’s post-hoc test ($P$-value $P<0.005$). In both types of analysis, the comparison was conducted separately on Class-I patients (Class I) and on patients whose outcomes were unreported or of Class II or above (Class I). Comparisons were then repeated on the combination of both sets of patients (All Patients).
While quantitative metrics of success are necessary for determining the viability of a classifier for the clinical setting, the results must have a clinical interpretation in order for it to be ultimately implemented. To determine if this was the case, those channels classified as probable SOZ were compared to the actual resected volume from the clinical notes. For each patient and decision system, the clinical significance of the predicted SOZ (P-SOZ) was assessed by measuring the similarity between P-SOZ and RV. Specifically, it was determined whether P-SOZ and RV coincided (P-SOZ ≡ RV), P-SOZ was included in RV but smaller than RV (P-SOZ ⊂ RV), P-SOZ was larger than RV and contained RV (RV ⊂ P-SOZ), or P-SOZ overlaps with RV (RV ∩ P-SOZ ≠ ∅ and RV ∩ P-SOZ ≠ ∅). For each scenario, a score of 0 was assigned if P-SOZ aligned with the reported RV or a score of (−n₁, +n₂) was assigned if P-SOZ did not include n₁ channels that were part of the RV and included instead n₂ channels that were not part of the RV. The error rate was computed as the ratio between the number of mislabeled channels n₁+n₂ and the total number of channels.

In general, little attention is paid to the level of surgical success, which is analogous to accuracy of surgical planning in determining SOZ, when selecting patients for inclusion in training or testing data. Misidentified channels in a clinical report could therefore bias the results of a classifier. Therefore, the composition of the training sets with Class I patients reflects the assumption that only cases with a successful post-surgery outcome should be used as “gold standard”. The influence of training set “quality” on the overall performance was tested by designing a second rank-based SVM classifier (Rank-based SVM-All). It was designed as the Rank-based SVM and was evaluated through a K-fold cross-validation procedure (K = 8) as before but, in this case, each training set consisted of a combination of both successful patients (Class I) and unsuccessful or partially successful patients (Class >I, the last six patients in
TABLE 3.2). Each combination was chosen randomly, with no constraints on the number of Class I and Class >I patients used. It was guaranteed, instead, that each patient was included in a validation set at least 3 times (average: 4.43±0.65; min: 3, max: 5). In case of Class >I patients, the training was conducted on the RV. For each classifier and patient in the validation sets, both the aggregated analysis and the window-based analysis for Rank-based SVM-All were performed and compared to the results for Rank-based SVM (one-way ANOVA test, P-value P<0.01).

3.3 Results:
3.3.1 Dataset
To develop, train, and test the proposed classifier, fourteen patients with drug-resistant epilepsy from the iEEG Portal were processed for HFO detection. A total of 8 out of 14 selected patients had temporal lobe epilepsy and 6 had extra-temporal lobe epilepsy (5 had frontal lobe epilepsy, 1 had parietal lobe epilepsy). Five out of 14 patients had a reported etiology (3 meningitis, 1 dysplasia, 1 traumatic brain injury) and 9 had epilepsy of cryptogenic origin.

Eleven out of 14 patients underwent at least one resective surgery and were classified according to the Engel or ILAE classification scale 12 months-post surgery at a clinical follow-up evaluation. If the patient received multiple surgeries, the combination of resected volumes was considered as the most likely approximation of the SOZ and the classification resulting from the last surgery was used to assess surgical success. Patients were Engel/ILAE Class I (8 patients), Class IV (2 patients), or Class V (1 patient) at the follow-up. Three (3) patients (Study_10, Study_11, and HUP_70) did not undergo surgery after the presurgical monitoring. The CD-SOZ was considered a probable
approximation of the seizure onset zone in these patients and used in lieu of the RV. These patients were labeled as “unsuccessful” cases because surgery was deemed not a viable option for them and analyzed along with the partially successful surgical cases (Class II or above). A total of 172.7±90.1 h of continuous iEEG recordings per channel and patient were analyzed (min: 48 h; max: 310 h), with an average number of 75.6±23.4 electrodes per patient. The RV spanned an average of 10.2±2.6 electrodes per patient, which correspond to an average fraction of 0.25±0.23 of the electrodes per patient. Comprehensive patient-specific information can be found in TABLE 3.2.

### TABLE 3.2

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Sex/Age (y)</th>
<th>Seizure Onset Zone</th>
<th>Etiology</th>
<th>Seizure Type</th>
<th>No. of Seizures</th>
<th>iEEG electrodes (depth/strip/grid)</th>
<th>iEEG recordings (h)</th>
<th>Post-surgery Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study_005</td>
<td>M / 26</td>
<td>Right Temporal</td>
<td>Cryptogenic</td>
<td>CP</td>
<td>77</td>
<td>16 / 0 / 0</td>
<td>160</td>
<td>ILAE-I</td>
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<td>Left Frontal</td>
<td>Cryptogenic</td>
<td>CP / GTC</td>
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<td>0 / 8 / 48</td>
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<td>Right Temporal</td>
<td>Cryptogenic</td>
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<td>3</td>
<td>0 / 36 / 48</td>
<td>84</td>
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<td>Cryptogenic</td>
<td>CP / GTC</td>
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<td>277</td>
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<td>Meningitis</td>
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<td>ILAE-IV</td>
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<td>8 / 28 / 60</td>
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<td>8 / 16 / 64</td>
<td>48</td>
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<td>0 / 56 / 0</td>
<td>146</td>
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</table>

Patient ID= unique identifier in the iEEG Portal database. TBI= traumatic brain injury. CP= complex partial seizure. GTC= generalized tonic-clonic seizure. SP= simple partial seizure. n/a= no follow-up available.
3.3.2 Analysis of HFO Rate vs Susceptibility Index

The HFO detection was performed independently on every iEEG channel. The average HFO rate per channel was calculated in each patient and resulted in 0.88±0.49 events/min for channels in the RV and 0.56±0.24 events/min for channels outside the SOZ (non-SOZ channels), mean ± S.D. The increment of the HFO rate in the RV channels versus non-SOZ channels was significant at the group level (Wilcoxon rank-sum test) both when the group included the entire set of patients in TABLE 3.2 (P-value P=0.03) or Class I patients only (P=0.01), while the difference was nonsignificant for patients with partially successful or unreported outcomes (Class >I, P=0.34). At the individual-level, instead, the HFO rates for RV channels and non-SOZ channels were comparable (Fig. 3.4A), with the rate for RV channels lower than non-SOZ channels in 2 out of 14 patients (Fig. 3.4A, green bars) and nonsignificant differences between Class I and Class >I patients. The proposed susceptibility index, instead, had an average value of 0.08±0.02 for RV channels and 0.03±0.02 for non-SOZ channels across patients (mean ± S.D.) with

![Figure 3.4](image)

**Fig. 3.4** HFO rate versus susceptibility index S. A-B) Average value of the HFO rate (A) and the susceptibility index (B) across RV channels (red) and non-SOZ channels (black) computed for each patient. Average is reported as mean (square dots) ± S.D. (vertical bars). Asterisks and diamonds denote difference between RV and non-SOZ channels (Wilcoxon rank-sum test) with P-value P<0.05 and P<0.005, respectively. Green bars indicate cases where the average value is higher for non-SOZ channels than RV channels. Patient IDs in B) and D) also apply to A) and C), respectively. C-D) Fano factor of HFO rate (C) and susceptibility index (D) estimated for each patient. Color code in A-B) also applies to C-D). Dashed, vertical lines separate Class I patients (Class I) from patients with partially successful or unreported post-surgery outcomes (Class >I).
significant differences at the group level for the three groups *All Patients*, *Class I*, and *Class >I*, respectively (Wilcoxon rank-sum test, $P$-value $P<0.001$). This trend was consistent across patients (Fig. 3.4B), with susceptibility values significantly higher for RV channels than non-SOZ channels in 13 out of 14 patients (see asterisks and diamonds in Fig. 3.4B).

The dispersion of both HFO rates and susceptibility indices around their mean values was quantified by the Fano factor (3.4C-D), which is defined as the ratio between variance and mean. Higher values of Fano factor indicate a greater dispersion of the probability distribution. The Fano factor of the HFO rates varied largely according to the patient and channel, with no specific trend for RV versus non-SOZ channels nor among patient groups (Fig. 3.4C). The susceptibility index, instead, had a significantly lower Fano factor than the HFO rate both in case of RV and non-SOZ channels (Fig. 3.4D). Moreover, the factor values of RV and non-SOZ channels were comparable in each patient and across patients, which indicates that the susceptibility index had similar probability distributions across patients and types of channels.

![Separability SOZ versus non-SOZ Channels](image)

Fig. 3.5 Separability between RV channels and non-SOZ channels measured by using the z-score when the HFO rate (gray squares) or the susceptibility index (black dots) is used. Values are computed individually for each patient. A dashed, vertical line separates *Class I* patients (left side) from *Class >I* patients (right side).

The z-score, a standardized measure of distance, between the average elements in vectors $S_k$ and $F_k$ for RV and non-SOZ channels was used to compare the separability between SOZ and non-
SOZ channels by using the raw HFO rate or the susceptibility index. Denoted with $\mu_{v,loc}$ and $\sigma_{v,loc}$ the sample mean and standard deviation of the elements $v$, respectively, in vectors $S_k$ ($v = s$) or $F_k$ ($v = f$) for RV channels ($loc = RV$) or non-SOZ-channels ($loc = NSZ$), the z-score was defined as:

$$\Delta_v = \log \left| \frac{\mu_{v,RV} - \mu_{v,NSZ}}{\sigma_{v,NSV}} \right|$$

for $v = s$ and $v = f$. A comparison between the values of $\Delta_s$ and $\Delta_f$ for each patient (Figure 3.5) indicates that the average separation between the RV and non-SOZ channels was larger for the susceptibility values ($\Delta_s$) than the rate values ($\Delta_f$) in 14 out of 14 patients, which suggests that the proposed transformation contributes to better separate the epileptogenic channels. Moreover, values of $\Delta_s$ in Class I and Class >I patients were compared and showed that $\Delta_s$ is larger in Class I patients (4.5±0.8 versus 3.5±1.2, Class I versus Class >I, mean ± S.D.), which suggests that the channel separability was larger for the successful cases.

3.3.3 Aggregate and Window-based Classifier Performance

Fig. 3.6 summarizes the results of the aggregated analysis (Fig. 3.6A-B) and window-based analysis (3.6C-D) conducted for Rank-based SVM, Rate-based SVM, and Rank-based LR on

![Image](image_url)

Fig. 3.6. A-B) Aggregated analysis. ROC curves (lines) and 95% confidence intervals (vertical bars) estimated on patients Study_21 (A) and HUP_68 (B), respectively, for Rank-based SVM (blue), Rate-based SVM (red), and Rank-based LR (green). C-D) Window-based analysis. Area under the ROC curve (lines) and 95% confidence intervals (strips) estimated over consecutive windows (sliding by one 10-min-long epoch) on patients Study_21 (C) and HUP_68 (D), respectively, for Rank-based SVM (blue), Rate-based SVM (red), and Rank-based LR (green). TPR (FPR)= true (false) positive rate; AUC=area under the ROC curve.
validation sets Study_21 and HUP_68. Each decision support system was trained on either the rank vectors or the rate vectors from 120 interictal epochs from Class I patients.

3.6C and 3.6D show the time-dependent average ROC curves (±95% confidence intervals) estimated for each decision support system on a total of 546 epochs (Study_21) and 633 epochs (HUP_68), respectively. In both examples, the average value of the area under the ROC curve (AUC) was 0.94 and the proposed Rank-based SVM significantly outperformed Rate-based SVM in precision (PPV), sensitivity (TPR), AUC, and accuracy (ACC), ANOVA with Tukey-Kramer post-hoc test ($P$-value $P<10^{-4}$). The trend was consistent across the cohort of Class I patients, was observed in Class >I patients, and remained consistent at the group level ($P$-value $P<0.005$). The average values of AUC, TPR, PPV, and ACC for Rank-based SVM ranged between 0.86 and 0.94 for Class I patients and was lower (range: 0.71-0.90) for Class >I patients, with no significant difference between the two patient groups. The Rate-based SVM classifier (red lines, 3.6A-B), performed at the chance-level consistently across all patients, with no significant difference at the group level between Class I patients and Class >I patients. Overall, these results suggest that the proposed susceptibility index increased the separation between the RV-related features and the non-SOZ-related features and facilitated the classification.

It was also tested whether the classification performance was entirely determined by the susceptibility index vector or rather influenced by the use of SVM. The logistic regression classifier was applied to susceptibility vectors (Rank-based LR) and compared the results to those of Rank-based SVM. Fig. 3.6A-B demonstrates that the Rank-based LR classifier provided superior performance than Rate-based SVM in each patient and at the group level ($P$-value $P<0.005$) but remained significantly lower than Rank-based SVM both at the level of individual patients and at the group level. Overall, these results suggest that the use of classification routines of higher
complexity (e.g., SVM versus logistic regression) further increased the classification performance, with an average increment of 28% in AUC values at the group-level (Class I patients) and even more significant increments in accuracy, sensitivity, and PPV.

The ability of the Rank-based SVM decision system to predict the SOZ in a realistic surgery planning scenario was assessed. To this end, each validation set from Class I patients was divided into consecutive three-epoch-long windows, sliding by one epoch, and the ROC curve analysis of each decision support system was repeated on every window individually, i.e., the reliability of the classification if based on as little as 30 minutes of data (i.e., three consecutive epochs). 3.6C and 3.6D report the average AUC value for every window over a total of 72 h (432 windows) of continuous iEEG recordings in Study_21 and HUP_68, respectively. In both patients, Rank-based SVM resulted in an average AUC value of 0.94 and remained consistently above 0.90 over time while Rate-based SVM performed close to chance-level (i.e., AUC=0.5). Rank-based LR, instead, had performance well above chance level but significantly lower than Rank-based SVM in each window. The trend in 3.6C-D was consistent in all Class I patients and led to the population-average performance reported in TABLE 3.3. Rank-based classifiers Rank-based SVM and Rank-based LR outperformed the Rate-based SVM classifier (P-value P<10^{-8}) in terms of AUC, sensitivity, PPV, and accuracy in Class I patients and had a similar trend in Class >I patients, despite lower average values. Moreover, Rank-based SVM outperformed Rank-based LR in each patient and, on average, the values of AUC, ACC, TPR, and PPV estimated for Rank-based SVM were significantly higher than the correspondent values for Rank-based LR in 393.4±48.7, 387.3±64.2, 283.2±39.6, and 390.8±52.4 out of 432 windows, respectively (mean ± S.D. across patients),
which suggest that this solution has promise for unsupervised pre-surgical SOZ identification.

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<th>Patient ID</th>
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Sens. = sensitivity; Spec. = specificity; Accu. = accuracy; values are reported as mean (S.D.) across $M=5$ classifiers. Class I = average across Class I validation patients; Class $>1$ = average across validation patients of Class II or above or patients without post-surgery follow-up; All patients = average across all validation sets. Symbols *, §, and ‡ denote a significant difference Rank-based SVM versus Rate-based SVM, Rank-based SVM versus Rank-based Logistic Regression, and Rate-based SVM versus Rank-based Logistic Regression, respectively (two-way ANOVA test with Tukey’s post-hoc test, P-value $P<0.005$). For each combination of patient and metric, the highest value is reported in bold font.
3.3.4 Theoretical Clinical Assessment

For each patient in the validation set, the clinical relevance of Rank-based SVM was assessed by counting the number of mislabeled EEG electrodes. Each validation set (Class I patients) was divided into consecutive three-epoch-long windows as done before for the Window-based Analysis and, for each window, a score was assigned to the Rank-based SVM prediction. Two examples of predicted SOZ (P-SOZ) provided by Rank-based SVM after processing a single window of data (30 minutes) are reported in Fig. 3.7A-B. The prediction scores for patients HUP_68 and Study_16 are 0 and (0, +2), respectively. For each Class I patient, the average error rate across the windows was generally low and consistent across patients (Fig. 3.8A). Moreover, the prediction error significantly increased when Rank-based SVM was tested on Class >I patients (error rate: 6.5±1.1% versus 12.8±1.2%, Class I patients versus Class >I patients, Wilcoxon rank sum test, P-value P<0.0007, see 3.8A), thus indicating that the predicted SOZ was substantially different than the RV in unsuccessful cases.

At the group-level, Class I patients and Class >I patients were considered separately and, for each group, the average fraction of patients across the validation sets for whom the prediction score was 0, (−n₁, 0) with n₁>0 (P-SOZ ⊆ RV), (0, +n₂) with n₂>0 (RV ⊆ P-SOZ), or (−n₁, +n₂) with n₁, n₂>0 was determined. In Class I patients, Rank-based SVM predicted the RV exactly in 4
out of 8 patients (46% of the total number of validation sets, Fig. 3.8B) and underestimated the RV by approximately 1 electrode in the other 4 patients (average score: (-1.2,0), 51% of the total number of validation sets, Fig. 3.8B). In only a few cases (3% of the total, Fig. 3.8B), the prediction was either larger than the RV or shifted when compared to the RV. The overall performance significantly decreased when Rank-based SVM was tested on Class >I patients. In this case, the predicted SOZ was larger than the RV in 1 out of 6 patients (20% of sets, average score: (0, +1.2), Fig. 3.6B) and shifted in 5 out of 6 patients (79% of sets), with an average of 2.4 mislabeled channels per patient (average score: (-1.0,+1.4), Fig. 3.8B). This is expected because the removal of the RV region in Class >I patients did not prevent the patients from having seizures.

The prediction performance of Rank-based SVM on Class I patients was significantly better than the performance of Rank-based SVM-All, which was obtained by training the Rank-based
SVM system on a combination of Class I and Class >I patients. As reported in Fig. 3.8C, the predicted SOZ provided by Rank-based SVM-All had a poor overlapping with the RV, with average error between 2 to 4 electrodes, which correspond to an average of 3 to 7 cm², and no significant difference between Class I and Class >I patients. Overall, these results indicate that the Rank-based SVM system selectively agreed with the RV only in patients with successful post-surgery outcomes regardless of the epilepsy etiology, type of seizures, and electrode configuration. To achieve this result, though, a combination of “gold standard” cases was required during the training phase.

3.4 Discussion:
Numerous previous attempts to perform unsupervised identification of the seizure onset zone have been tried, but a solution to this challenging engineering problem remains elusive. A central obstacle to success in this endeavor is the exceptionally high degree of variability in disease etiology and seizure type among patients. This variability complicates efforts to define quantitative features of the SOZ in the epileptic brain consistently across patients, stunting efforts to develop universal and thus generally useful solutions. Studies utilizing network-based features have seen some limited success in solving the problem; these efforts have been limited to epilepsy occurring in the temporal lobe and are dependent on peri-ictal data. Others have used time-frequency analysis, but performance is inconsistent on interictal data and cases without clear lateralization. As a result, these approaches have had limited application for surgical planning.

A different approach is clearly needed. The described approach compensates for high inter-patient variability by ranking the iEEG channels according to the level of high frequency activity. This method attempts to take advantage of the observation that, in the epileptic brain, HFO are often more frequent in the SOZ than the rest of the brain network, in a way that is consistent across
patients, which allows rank to act as a feature that can be applied across patients with very different baseline HFO rates. Similarly, the large fluctuations in HFO rate within the same patient during the sleep-wake cycle are addressed by the combination of rank and consensus, based on the observation that, while HFO rate may be very noisy frame-to-frame, SOZ are among top channels a greater portion of the time.

In order to determine the viability of HFO as a tool to assist in clinical diagnosis, an automated classification system was developed to provide patient- and patient-state independent labeling of iEEG channels as SOZ or non-SOZ, with the success of the system providing proof of the ultimate utility of the HFO for this purpose. The system detects ripple events in multi-channel iEEG time series and determines the channel most likely to be SOZ-related by combining a machine learning feature based on transformed channel rankings and SVM classification. Tested on over 2,400 hours of continuous multi-channel recordings from fourteen patients with various combinations of disease etiology, seizure onset zones, and electrode configurations, this tool correctly identified the resected volume in patients with successful post-surgery outcomes (Class I) using as little as 30 minutes of iEEG data and no prior information about the patient’s condition. The performance was consistent across all Class I patients, insensitive to the patient’s sleep-wake cycle, and with average values of sensitivity, accuracy, and area under the ROC curve above 0.90, which correspond to less than one channel average difference between the predicted and resected volumes. By comparison to two alternative algorithms, the proposed solution shows that the combination of SVM classification and channel ranking can enhance precision, reliability, and robustness of the SOZ identification process against intra- and inter-patient variability, thus paving the way towards new tools for epilepsy surgery planning and clearly demonstrating that the diagnostic potential of HFO can be realized despite the challenges associated with their use.
Another reason for the current lack of unsupervised methods for SOZ identification is that, during the surgery planning, it is challenging to determine the most likely surgical outcomes associated with the estimated seizure onset zone. This is also reflected in this dataset, where no significant difference between Class I patients and Class >I patients was reported in terms of average HFO rate. Moreover, results of the aggregated analyses (Aggregated Analysis and Window-based Analysis) show that the average level of accuracy of these solutions had a similar order of magnitude in Class I and Class >I patients. Further analysis, though, demonstrated that the seizure onset zone predicted by the method was well aligned with the actual resected volume in Class I patients and significantly shifted in Class >I patients.

Metrics of classifier success (AUC, accuracy, etc) were high for both Class I and Class> I patient, with a large difference between the two groups. This finding is initially troubling, given the challenge in determining probable surgical outcomes from estimated SOZ. A high degree of agreement between predicted SOZ and the RV of an unsuccessful surgery would indicate a chance for poor outcomes from automated SOZ classification. However, a closer analysis of specific channels labeled SOZ in each patient demonstrated that the SOZ predicted by the method was well aligned with the actual resected volume in Class I patients and significantly shifted in Class >I patients. This subtle difference was overwhelmed in the success metrics by the high number of channels successfully labeled non-SOZ, hiding the shift of PD-SOZ in Class >I patients. This result is promising because it shows that a rank-based approach may help to better predict the success of the epilepsy surgery and provide a tool for decision support in the clinical setting. When applied to cases of unsuccessful surgery, the method shows that the area with sustained and stable HFO activity was either shifted or partially outside of the resected volume, suggesting that, by combining machine learning and a training strategy based on “gold standard” cases, it is possible
to achieve high accuracy in the estimation of the seizure onset zone, which may significantly help improve presurgical planning.
Chapter 4: Relationship between temporal arrangement of HFOs and epilepsy

4.1 Introduction

In this chapter, the goals described in aim 2 will be addressed. These goals include characterization of the temporal pattern of HFO occurrence by determination of the association of temporal pattern with SOZ channels, and investigation of possible links between temporal patterns and different subtypes of epilepsy.

4.2 Rationale for Investigation of HFO Temporal Pattern

The high variability of HFO events over time suggests the potential presence of non-stationary temporal variations in HFO occurrence, possibly linked to changes in underlying epileptogenic activity. This is supported by evidence that HFO rate varies so widely in time and space that the locations where HFOs are highest may change as frequently as once every few minutes, reinforcing the idea that HFO generation is a nonstationary process with significant differences in spatial distribution. Furthermore, the relatively broad source area of detected HFO ripples suggest that HFO arise from network oscillators, similarly to synchronized IPSPs in hippocampal interneurons (Jefferys et al. 2012). This mix of cellular and network mechanisms of HFO origin raise the possibility of characteristic patterns of HFO occurrence. It has been suggested that temporal pattern information may be one way to discriminate pathological and physiological HFO (J. Jacobs et al. 2012). Other applications, like SOZ localization or seizure prediction may be possible. However, there is currently a knowledge gap as it pertains to characterizing the evolution of HFOs over time. Furthermore, it is unclear whether the temporal pattern of the HFO events has features specific to the SOZ and if these features might help enhance the localization of the SOZ. Whether this phenomenon exists, can be captured, and has utility as a potential SOZ
biomarker has not yet been determined. This investigation will seek to determine whether HFOs are produced in a signature temporal pattern or occur purely as a stochastic process and whether the temporal pattern of HFOs manifests differently in the SOZ versus the rest of the brain. It will also seek to determine if there is any pattern consistent to types of epilepsy or location of focal area.

4.3 Methods

4.3.1 Patient Selection and HFO Detection

Twenty de-identified patients with drug-resistant focal epilepsy were selected for inclusion from the iEEG.org portal. Subjects were included according to two criteria, i.e., (i) a clinical report was available on the iEEG Portal with information about the epilepsy etiology, type of seizure, age at the time of the epilepsy surgery, and estimated SOZ, and (ii) at least two continuous days of iEEG recording were collected. Recordings were sampled at 512Hz and patients were monitored for 2 to 7 days. The reported SOZ was defined by board-certified epileptologists according to established guidelines (Rosenow and Lüders 2001). The clinically defined SOZ was used instead of the resected volume because the volume may include channels that were not involved in electrographic seizures. Recordings were processed for HFO detection using an existing algorithm described in (Gliske et al. 2016) as detailed in Chapter 3.

4.3.2 Point Process Modeling

Given the nonstationary and transient nature of the suspected pattern in HFO occurrence, a powerful statistical tool was necessary to capture the pattern from long iEEG recordings with high levels of variability. To this end, a Point Process Model framework was chosen. PPMs have a history as a well-established tool in computational neuroscience to analyze time-varying nonstationary binary time series like spike trains and have been used for the unsupervised detection of seizure onset. Established methods exist to optimally fit the PPM on a binary sequence, and
methods of statistical inferences about recurrent temporal patterns in a binary sequence from the estimated PPM parameters are accepted in the field. Using these methods, the temporal pattern of HFO occurrence can be well defined and useful comparison can be made between groups.

With this framework established, the PPM was implemented as follows. For each channel \(c\), detected HFOs were defined as discrete events that occur in continuous time. Denoted with \(u_{c,j}\) the onset time of the \(j\)-th HFO in the channel over the observation interval \((0, T]\), the sequence of times \(0 < u_{c,1} < ... < u_{c,j} < ... < u_{c,J} \leq T\) defines a point process. In a point process, the probability that an event occurs at any time \(t \leq T\) depend on the state at time \(t\) as well as the sequence of events before \(t\), i.e., \(H_{c,j} = \{u_{c,j} < t, \ i = 1, 2, 3,...\}\), and is uniquely determined by the conditional intensity function (CIF)(Kass, Eden, and Brown 2014):

\[
\lambda_{c,j} = \lim_{\Delta t \to 0} \frac{P\left(N_{c,(t, t+\Delta t]} = 1\mid H_{c,j}\right)}{\Delta t},
\]

where \(N_{c,(t, t+\Delta t]}\) is the number of events occurring in the channel in the interval \((t, t+\Delta t]\) and \(P(\cdot | \cdot)\) denotes the conditional probability function. A point process generalizes the Poisson process to include cases where the increments \(N_{c,(t, t+\Delta t]}\) are nonstationary and history-dependent. The CIF allows determination of a point process because it informs the joint probability of the sequence \(0 < u_{c,1} < ... < u_{c,J} \leq T\) according to the formula(Kass, Eden, and Brown 2014):

\[
P(u_{c,1}, u_{c,2}, ..., u_{c,J}) = \exp\left(-\int_{0}^{T} \lambda_{c,t} dt\right) \prod_{j=1}^{J} \lambda_{c,u_{c,j}},
\]

and a point process model (PPM) is a parametric representation that expresses \(\lambda_{c,t}\) at any time \(t\) as a function of \(t\) and the event history up to \(t\) to maximize the joint probability (2)(Kass, Eden, and Brown 2014). To find the appropriate PPM, the recording horizon was divided into consecutive, nonoverlapping bins of size \(\Delta t = 1s\) and defined the model structure:
\[
\lambda_{c,k} = \exp\left\{ \alpha_c + \sum_{i=1}^{M} \beta_{c,i} N_{c,(k-h_{i,1},k-h_{i,2})} \right\},
\]  \hspace{1cm} (3)

where \( \lambda_{c,k} = \lambda_{c,k} \) is the CIF value at the midpoint \( t_k \) of bin \( k \) and \( N_{c,(k,h)} \) is the increment from bin \( k \) to bin \( h \). The bin size \( \Delta t \) was chosen to guarantee that every HFO spanned no more than one bin and the recording horizon was therefore discretized into a sequence of binary increments \( N_{c,(k,k+1)=0,1} \). Under this condition, loglinear models provide a discrete-time approximation of (1) and can be fitted on the binary sequence \( \{N_{c,(k,k+1)}\}_k \) using maximum likelihood methods. Furthermore, the probability of having an HFO in the generic bin \( k \) is approximately \( \lambda_c \Delta t \), and a statistical testing procedure (i.e., the Kolmogorov-Smirnov [K-S] test applied on time-rescaled inter-event intervals) is available to determine the goodness-of-fit of a PPM on the binary sequence \( \{N_{c,(k,k+1)}\}_k \).

The loglinear model described in (3) defines regressive models with \( M \) explanatory variables, where each variable indicates the number of events that occurred in a specific time interval before bin \( k \). Each model \( M_c \) is parametrized in the vector \( \theta_{M_c} = [\alpha_c, \beta_{c,1}, \beta_{c,2}, \ldots, \beta_{c,M}] \), where \( \alpha_c \) is the logarithmic background rate of HFOs in channel \( c \) if there was no prior HFO in the intervals spanned by the \( M \) variables.

For each patient and channel, the PPM class was sampled by varying the number \( M \) of variables (\( 0 \leq M \leq 12 \)) and width \( h_{i,2} - h_{i,1} \) of the intervals \( N_{c,(k-h_{i,1},k-h_{i,2})} \), for \( i=1,2,\ldots, M \), \( (h_{i,2} - h_{i,1} \) ranging from 1s to 120s). A total of 56 loglinear models were considered, with each model spanning a total history window \( W \) that ranged between 10 seconds and 30 minutes. Each model was fitted on 80% of the binary sequence \( \{N_{c,(k,k+1)}\}_k \) (training set) and tested on the remaining 20% (testing set). Only models that passed the K-S test on the testing set at the 95% significance value (i.e., \( P \)-value \( P<0.05 \)) were further considered. The final model structure (i.e., the combination of values \( M, h_{i,1}, \) and \( h_{i,2}, \) for \( i=1,2,\ldots, M \)) was chosen among the 56 models that

<table>
<thead>
<tr>
<th>Interval</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>( h_{i,1} ) (seconds)</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>( h_{i,2} ) (seconds)</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>120</td>
</tr>
</tbody>
</table>

Table 4.1. History Window Structure of Final PPM
passed the K-S test by minimizing the average Akaike information criterion across the channels and patients (Akaike 1974). History windows for the selected model are in TABLE 4.1.

4.3.2 Statistical Methods for HFO Pattern Inference and Data Analysis

The optimal model structure chosen with the above procedure was fit to data in each channel $c$ and the resultant parameter sets (one set per channel) were used to infer recurrent patterns in the sequence of HFO events in $c$. The 95% confidence intervals of each optimal parameter $\hat{\beta}_{c,i}$ was calculated and parameters $\hat{\beta}_{c,i}$ either of 2 conditions, the lower 95% confidence bound of $\exp\left\{\hat{\beta}_{c,i}\right\}$ was greater than 1.05 or the upper 95% confidence bound of $\exp\left\{\hat{\beta}_{c,i}\right\}$ was lower than 0.95, were identified as parameters indicating a meaningful pattern.

These conditions are dependent on the observation that for $\exp\left\{\hat{\beta}_{c,i}\right\} > 1$ the occurrence of HFO events in the interval $(k-h_{i,1}, k-h_{i,2}]$ in (3) increases the likelihood of observing a HFO in the bin $k$. Vice versa, any $\hat{\beta}_{c,i} < 0$ would result in $\exp\left\{\hat{\beta}_{c,i}\right\} < 1$ and therefore lower the likelihood of observing a HFO in the bin $k$, provided that HFOs were observed in $(k-h_{i,1}, k-h_{i,2}]$. Accordingly, the first enhancement condition indicates that the occurrence of HFOs in $(k-h_{i,1}, k-h_{i,2}]$ increases the likelihood of observing an HFO in the bin $k$ by 5% or more and that such increment is significant at the 95% level (i.e., $P$-value $P<0.05$). The second reduction condition, conversely, means that the occurrence of HFOs in $(k-h_{i,1}, k-h_{i,2}]$ lowers by at least 5% the chance of observing an HFO in the bin $k$. Note that increments and decrements are related to the chance of an HFO determined by the average HFO rate. Furthermore, the log-linear structure of (3) determines that the satisfaction of the enhancement condition on multiple variables $\hat{\beta}_{c,i}, i=i_1, i_2, i_3, \ldots$, in the same model strongly increases the likelihood of observing an HFO in the bin $k$ if HFOs occur in all the relevant intervals $(k-h_{i,1}, k-h_{i,2}], i=i_1, i_2, i_3, \ldots$. Hence, any combination $\hat{\beta}_{c,i_1}, \hat{\beta}_{c,i_2}, \hat{\beta}_{c,i_3}, \ldots$ that satisfy the enhancement
necessarily implies the presence of a recurrent pattern in the temporal arrangement of the HFO events.

For each patient and channel, the combinations of values $\hat{\beta}_{c,d}$ satisfying either the enhancement or reduction condition were isolated and, for each combination, the number of repetitions in each patient as well as the average value $\bar{\beta}_{c,d}$ in each patient were estimated. These results were aggregated for SOZ channels or non-SOZ channels, patients with epilepsy of temporal lobe origin (TLE) or extra-temporal origins (non-TLE). Group-level differences for the identified combinations were determined via two-way ANOVA with Tukey’s post-hoc test ($P$-value $P<0.05$) with variables being the type of channels (SOZ vs. non-SOZ) and the type of epilepsy (TLE vs. non-TLE).

HFO patterns detected by the PPM were tested to determine if there was a significant difference in SOZ versus non-SOZ channels at the level of individual patients. For each patient, $\theta_c$ denotes the vector of optimal parameters in (3) for a generic channel $c$ and vectors $\theta_c$ were grouped in two groups (i.e., SOZ channels and non-SOZ channels). For each group $g$ ($g=$SOZ or $g=$non-SOZ), the Euclidean distance $D_{c,g}$ between any vector $\theta_c$ and the centroid $C_g$ of the group and the cosine similarity $S_{c_1,c_2,g}$ between any pairs of vectors $\theta_{c_1}$ and $\theta_{c_2}$ in the group were computed. Metrics $D_{c,g}$ and $S_{c_1,c_2,g}$ estimate the level of dispersion of vectors $\theta_c$ in each group. For each group $g$, the intra-group dispersion was tested to determine the presence of significantly different dispersion across groups by comparing the sample distribution of values $D_{c,g}$ and $S_{c_1,c_2,g}$ to the values $\bar{D}$ and $\bar{S}$, respectively (Wilcoxon rank-sum test, $P$-value $P<0.05$), where $\bar{D}$ and $\bar{S}$ are the average normalized Euclidean distance and cosine similarity, respectively, between any two vectors $\theta_a$ and $\theta_b$, with $\theta_a$
from the SOZ group and $\theta_s$ from the non-SOZ group. The two groups were well-separated if the metrics of intra-group dispersion are lower than the metrics of inter-group dispersion.

Finally, for each group and patient, the parameter vectors were tested to determine if they form one cluster or were separable into smaller clusters. The Dunn index was used to measure the cluster quality, including both intra-cluster dispersion and inter-cluster separation. More commonly used to determine the optimal number of clusters for a given problem, the Dunn index can be used to assess the relative cluster quality of different conditions of similar data in a case with a known number of clusters (i.e., SOZ and non-SOZ). Group variability was determined based off all 4 factors, as Euclidean distance from centroid (group dispersion), cosine similarity (intra-group similarity), distance between group centroids (inter-group separation), and Dunn index (group “quality’), to provide a complete assessment of clustering quality.

The variation in SOZ vs non-SOZ channels between pathology location was also investigated at the group level. Comparisons were performed to differentiate between patients with TLE and NTLE. Patients were separated into two groups, i.e., TLE and NTLE. For each group $l$ ($l = \text{TLE or NTLE}$), the analysis of the difference between CD-SOZ and non-SOZ channels was repeated to determine dispersion, separation, and cluster quality based on the average parameter value within each group $l$.

4.3.3 Methods to assess the value of point process model parameters in SOZ localization

To determine whether PPM parameter vectors as a representation of the temporal pattern of HFOs improved differentiation of CD-SOZ and non-SOZ clusters over the simple raw rate of HFO occurrence, the above analyses was repeated on the rate of ripple events and compared the results to those of the average PPM parameter vectors for groups $l$, again comparing between TLE and NTLE. To do so, the entirety each iEEG time series was divided into $N$ consecutive, non-overlapping, 10-min-long windows and the rate of ripple events in each window was estimated as
the average number of ripples per minute in that window. Then, for each channel \( c \), the vector of ripple rates \( \mathbf{R}_c = [r_{c,1}, r_{c,2}, \ldots, r_{c,w}] \), where \( r_{c,w} \) is the rate in the \( w \)-th window, was used to calculate the Euclidean distances \( D_{c,k}^r \) and cosine similarities \( S_{i,j,k,l}^r \) for rate vectors in each group combination, and the significance of the dispersion between vectors \( \mathbf{R}_c \) in each group was tested as described above for vectors \( \mathbf{\Theta}_c \). Average values of \( S_{i,j,k,l} \) and \( S_{i,j,k,l}^r \), the average values of \( D_{c,k,l} \) and \( D_{c,k,l}^r \) (normalized by the vector size, i.e., 10 and \( N \) for \( D_{c,k,l} \) and \( D_{c,k,l}^r \), respectively), and the correspondent centroid distances were compared. The Dunn index was also applied as described above for rate vectors \( \mathbf{R}_c \). Because the Dunn index functions as a ratio, values were not normalized for this analysis.

4.4 Results:
4.4.1 Dataset

These experiments included 20 patients with drug-resistant epilepsy from the iEEG Portal. Ten out of 20 patients had temporal lobe epilepsy and 10 out of 20 patients had extra-temporal lobe epilepsy (8 frontal, 1 parietal, 1 perirectal). Six out of 20 patients had a reported etiology (3 meningitis, 1 dysplasia, 2 traumatic brain injury) and 14 had epilepsy of cryptogenic origin. Every patient underwent normal planning for a minimum of one resective surgery, resulting in a complete clinical report and assessment and 11 out of 14 were classified according to the Engel classification scale or the ILAE classification scale at the 12 months-post surgery follow-up evaluation. If the patient received multiple surgeries, we considered the combination of resected volumes as the most likely approximation of the SOZ and we referred to the classification assigned at the follow-up visit that followed the last surgery. Patients were Engel/ILAE Class I (8 patients), Class IV (2 patients), or Class V (1 patient) at the follow-up. Details about patient-specific clinical information, disease etiology, and iEEG recording setup are in Table 4.2. A total of 173.2±98.1 h of continuous iEEG
recordings per channel and patient were analyzed (min: 48 h; max: 310 h), with an average number of 76.3±22.2 electrodes per patient. The RV (CD-SOZ in Study_010, Study_011, and HUP_70) spanned an average of 10.8±2.9 electrodes per patient, which corresponds to an average fraction of 0.23±0.21 of the available electrodes per patient.

4.4.2 HFO Rate and Separability
The HFO detection was performed independently on each EEG channel. The average HFO rate per channel was computed in each patient and resulted in 0.94±0.53 events/min for channels in the RV and 0.59±0.25 events/min for channels outside the SOZ (non-SOZ channels), mean ± S.D. The difference between the HFO rate in the RV channels versus non-SOZ channels was significant.

### TABLE 4.2

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Sex/Age (y)</th>
<th>Seizure Onset Zone</th>
<th>Etiology</th>
<th>Seizure Type</th>
<th>No. of Seizures</th>
<th>iEEG electrodes (depth/strip/grid)</th>
<th>iEEG recordings (h)</th>
<th>Post-surgery Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study_005</td>
<td>M / 26</td>
<td>Right Temporal</td>
<td>Cryptogenic</td>
<td>CP</td>
<td>77</td>
<td>16 / 0 / 0</td>
<td>160</td>
<td>ILAE-I</td>
</tr>
<tr>
<td>Study_011</td>
<td>F / 34</td>
<td>Right Temporal</td>
<td>Cryptogenic</td>
<td>CP</td>
<td>3</td>
<td>0 / 36 / 48</td>
<td>84</td>
<td>n/a</td>
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<tr>
<td>Study_012-2</td>
<td>M / 33</td>
<td>Right Temporal Orbitofrontal</td>
<td>Cryptogenic</td>
<td>CP / GTC</td>
<td>28</td>
<td>0 / 24 / 60</td>
<td>277</td>
<td>ILAE-I</td>
</tr>
<tr>
<td>Study_016</td>
<td>F / 36</td>
<td>Right Temporal Orbitofrontal</td>
<td>Meningitis</td>
<td>CP / GTC</td>
<td>3</td>
<td>0 / 16 / 48</td>
<td>141</td>
<td>ILAE-IV</td>
</tr>
<tr>
<td>Study_019</td>
<td>F / 33</td>
<td>Left Temporal</td>
<td>Cryptogenic</td>
<td>CP / GTC</td>
<td>15</td>
<td>8 / 28 / 60</td>
<td>136</td>
<td>ILAE-V</td>
</tr>
<tr>
<td>Study_021</td>
<td>M / 16</td>
<td>Right Temporal Orbitofrontal</td>
<td>Cryptogenic</td>
<td>CP / GTC</td>
<td>11</td>
<td>0 / 8 / 96</td>
<td>155</td>
<td>ILAE-I</td>
</tr>
<tr>
<td>Study_023</td>
<td>M / 16</td>
<td>Left Temporal-Occipital</td>
<td>TBI</td>
<td>CP</td>
<td>3</td>
<td>8 / 16 / 64</td>
<td>48</td>
<td>ILAE-I</td>
</tr>
<tr>
<td>HUP_65</td>
<td>M / 36</td>
<td>Right Temporal</td>
<td>Cryptogenic</td>
<td>CP</td>
<td>3</td>
<td>0 / 16 / 64</td>
<td>304</td>
<td>n/a</td>
</tr>
<tr>
<td>HUP_68</td>
<td>F / 26</td>
<td>Right Temporal</td>
<td>Meningitis</td>
<td>CP / GTC</td>
<td>5</td>
<td>0 / 24 / 64</td>
<td>310</td>
<td>ENGEL-I</td>
</tr>
<tr>
<td>HUP_73</td>
<td>M / 39</td>
<td>Anterior Right Frontal</td>
<td>Meningitis</td>
<td>CP / GTC</td>
<td>5</td>
<td>0 / 56 / 0</td>
<td>146</td>
<td>ENGEL-I</td>
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<td>Study_006</td>
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<td>Cryptogenic</td>
<td>CP</td>
<td>5</td>
<td>0 / 8 / 48</td>
<td>27</td>
<td>n/a</td>
</tr>
<tr>
<td>Study_010</td>
<td>F / 13</td>
<td>Left Frontal</td>
<td>Cryptogenic</td>
<td>CP / GTC</td>
<td>2</td>
<td>0 / 8 / 48</td>
<td>304</td>
<td>n/a</td>
</tr>
<tr>
<td>Study_014</td>
<td>F / 33</td>
<td>Left Frontal</td>
<td>Cryptogenic</td>
<td>CP / GTC</td>
<td>8</td>
<td>0 / 16 / 88</td>
<td>136</td>
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</tr>
<tr>
<td>Study_020</td>
<td>M / 10</td>
<td>Right Frontal</td>
<td>Cryptogenic</td>
<td>CP / GTC</td>
<td>8</td>
<td>0 / 16 / 40</td>
<td>120</td>
<td>ILAE-IV</td>
</tr>
<tr>
<td>Study_026</td>
<td>M / 9</td>
<td>Left Frontal</td>
<td>Cryptogenic</td>
<td>CP</td>
<td>17</td>
<td>0 / 32 / 64</td>
<td>70</td>
<td>ILAE-I</td>
</tr>
<tr>
<td>Study_028</td>
<td>M / 5</td>
<td>Left Parietal</td>
<td>Cryptogenic</td>
<td>GTC</td>
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<td>0 / 16 / 80</td>
<td>40</td>
<td>ILAE-IV</td>
</tr>
<tr>
<td>Study_037</td>
<td>F / 62</td>
<td>Right Frontal</td>
<td>TBI</td>
<td>CP</td>
<td>8</td>
<td>0 / 16 / 64</td>
<td>215</td>
<td>n/a</td>
</tr>
<tr>
<td>HUP_64</td>
<td>M / 20</td>
<td>Left Frontal</td>
<td>Dysplasia</td>
<td>SP / GTC</td>
<td>1</td>
<td>0 / 24 / 68</td>
<td>307</td>
<td>ENGEL-I</td>
</tr>
<tr>
<td>HUP_70</td>
<td>M / 32</td>
<td>Left Perirolandical</td>
<td>Cryptogenic</td>
<td>SP</td>
<td>8</td>
<td>0 / 14 / 64</td>
<td>160</td>
<td>n/a</td>
</tr>
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<td>HUP_72</td>
<td>F / 27</td>
<td>Left Frontal</td>
<td>Cryptogenic</td>
<td>GTC</td>
<td>1</td>
<td>0 / 52 / 0</td>
<td>314</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Patient ID= unique identifier in the iEEG Portal database. TBI= traumatic brain injury. CP= complex partial seizure. GTC= generalized tonic-clonic seizure. SP= simple partial seizure. n/a= no follow-up available.
at the group level (Wilcoxon rank-sum test) across the entire set of patients (P-value P=0.04) or Class I patients only (P=0.01). SOZ and non-SOZ channels were not well differentiable based on HFO rate in neither TLE nor nTLE patients. TLE and nTLE patients were also not differentiable based on HFO rate. Figure 4.1 report the histogram of HFO interevent intervals (IEI). Minor bimodal characteristics of the distribution provides supporting evidence for the presence of a pattern possible to detect with PPM, while its insignificance highlights the transient nature of the pattern and the difficulty of detecting it though simple analyses.

![Figure 4.1 – HFO Interevent Interval (IEI) Histogram](image)

4.4.3 Point Process Model Fitting

A point process model (1) was fitted independently on the sequence of detected HFOs for each channel and patient. A model structure was selected that fit (1) passed the K-S test (P-value P<0.05) on the testing set and 2) minimized the AIC value (average value across channels of selected model: .0714). Resulting estimated parameters were compared between CD-SOZ channels and non-SOZ channels for each patient. In 20 out of 20 patients, in all channels, the likelihood of an HFO at any bin k was significantly increased if a HFO occurred in the previous 2 bins (i.e., 2 s), satisfying the enhancement conditions on $e^{\beta_{c1}}$. By inference, this indicates the presence of a bursting pattern of HFO activity at all iEEG recording sites, which were believed to be in the
irritative zone. Furthermore, in CD-SOZ channels of 8 of 10 TLE patients, the likelihood of a HFO at any bin k was also significantly increased if a HFO occurred in the intervals 20-30s and 50-60 s before k, satisfying enhancement conditions on $e^{\beta_{c,5}}$ and $e^{\beta_{c,8}}$, and indicating the presence of an inter-burst interval between 20 s and 30 s, with the interval 50-60s capturing the same inter-burst periodicity. In an additional, in CD-SOZ channels for 1 of 10 TLE patients, the likelihood of a HFO at any bin k was also significantly increased if a HFO occurred in the intervals 6-20s and 20-30 s before k, satisfying enhancement conditions on $e^{\beta_{c,4}}$ and $e^{\beta_{c,5}}$, which by inference suggests a similar but less stable inter-burst periodicity. In all cases, results were consistent across channels, with similarly significant results in 95% of channels in a given patient and channel group.

Inference analysis was also performed on the average CD-SOZ vs NSZ parameter values for two groups $l$ ($l =$ TLE or NTLE). Pattern findings above hold true at the population level. For TLE patients, in CD-SOZ channels, the likelihood of a HFO at any bin k was increased if a HFO occurred in the previous 2 bins (i.e., 2 s) or in the intervals 20-30 s and 50-60 s before k, indicating the presence of a ripple bursting activity (inter-burst interval: 2s) and a pattern of inter-burst intervals between 20s and 30s. In TLE non-SOZ channels, the likelihood of a HFO was only
enhanced if another HFO had occurred in the previous 2 s, indicating the presence of bursting activity, but not a distinct pattern of bursts. Conversely, for NTLE patients, in all channels, the likelihood of an a HFO occurring in a given bin $k$ was increased only if an HFO occurred in the previous 2 s, indicating a bursting pattern, but no inter-burst periodicity, even in CD-SOZ channels. Figure 4.2 reports the proportion of channels showing significant in the 20-30 s and 50-60 s parameter range. Only TLE SOZ channels show a high level of significance in these parameters. These patterns are reflected as a raster plot of HFO events in Figure 4.3 and 4.4. Red boxes highlight inferred pattern occurrence.
4.4.4 Separability by PPM parameters

Four measures of group distinctiveness between CD-SOZ and non-SOZ channels for each patient were assessed: average Euclidean distance from group centroid, $D_{c,w}$, average cosine similarity between in-group vectors $S_{i,j,w}$, distance between group centroids, and Dunn Index.

The level of group dispersion for each patient was determined by $D_{c,w}$ and $S_{i,j,w}$. Average results for $D_{c,w}$ and $S_{i,j,w}$ are reported in Figure 4.5A/B, respectively. In 9 out of 10 TLE patients, $D_{c,w}$ is significantly lower in CD-SOZ channels (ANOVA with Tukey-Kramer post-hoc test, $P$-value $P<0.05$), indicating a tighter grouping of channel parameters. Similarly, $S_{i,j,w}$ is significantly higher in CD-SOZ in 9 out of 10 TLE patients (ANOVA with Tukey-Kramer post-hoc test, $P$-value $P<0.05$), indicating greater similarity among CD-SOZ channels, as shown in Figure 4.6.

Additionally, for the CD-SOZ group, the values $D_{c,w}$ were, on average, significantly smaller than the average between-group value $\bar{D}=0.27$ (ANOVA with Tukey-Kramer post-hoc test, $P$-value $P<$
and the values $S_{i,j,w}$ were, on average, significantly larger than the average between-group value $\bar{S}=0.66$ (ANOVA with Tukey-Kramer post-hoc test, $P$-value $P< 0.01$). There was not a significant difference in $D_{c,w}$ and $S_{i,j,w}$ between CD-SOZ and non-SOZ for any NTLE patients, nor was there a significant difference from average between-group values $\bar{D}$ and $\bar{S}$. These trends were conserved at the population level. CD-SOZ $D_{c,w}$ and $S_{i,j,w}$ are significantly lower (ANOVA with Tukey-Kramer post-hoc test, $P$-value $P< 0.01$) and higher (ANOVA with Tukey-Kramer post-hoc test, $P$-value $P< 0.01$), respectively, in the TLE group than the NTLE group. The separation of CD-SOZ and non-SOZ channel groups were determined by the distance between the group centroids for each patient. We compared the average distance between TLE and NTLE patients. The distance between CD-SOZ and non-SOZ centroids was significantly higher for TLE patients than NTLE patients (ANOVA with Tukey-Kramer post-hoc test, $P$-value $P< 0.01$), with very small centroid distance for NTLE patients, indicating very poor separation between CD-SOZ and non-SOZ channels in these patients. These results are reported in Figure 4.7.

Figure 4.6 – Cosine Similarity (mean±S.D.) TLE=Left 10 Subjects, NTLE= Right 10 Subjects
To quantify the distinctiveness of CD-SOZ and non-SOZ channels, the Dunn index, $DI$, was computed for each patient. A high $DI$ indicates well-separated and tightly clustered groups. The average $DI$ value for each group is reported in Figure 4.8. $DI$ was significantly higher for TLE patients than NTLE patients. Furthermore, the $DI$ value for the parameters averaged across each group were 3 times higher in the TLE group, indicating high quality parameter grouping at both the individual and population levels.

To show that the separation of CD-SOZ and non-SOZ in TLE patients was a result of the specific temporal pattern and not related to the simple HFO rate, rate vectors defined as the average HFO rate over each 10-minute bin for each channel for each patient were computed and the grouping analyses described above was repeated. White bar in Figure 4.7 reports group-level results for centroid distance on the HFO rate vectors. At both the group and individual levels, for all patient groups, there was no significant difference between CD-SOZ and non-SOZ channels when using HFO rate vectors. This suggests that PPM parameters (i.e., the temporal pattern of HFOs) better
distinguish CD-SOZ and non-SOZ channels than raw HFO rate.

4.5 Discussion

The purpose of this study was to address the goals described in aim 2. Point process modeling was used to identify a previous unknown pattern to HFO occurrence in the SOZ of TLE patients and demonstrate that this pattern was lacking in non-SOZ channels of TLE patients, and missing entirely from patients with focal areas outside the temporal lobe. The temporal characteristics of this pattern were described and the extent to which this pattern uniquely identifies SOZ channels we determined by cluster quality analysis.

The precise origins of HFO in the brain and the nature of their relationship to seizure onset is still not fully understood(Jefferys et al. 2012; J. Jacobs et al. 2012; Frauscher et al. 2017). Currently, it hypothesized that they arise from a combination of cellular and network processes, driven by synchronized activity of principal cells and interneurons(Das et al., n.d.; Jefferys et al. 2012; Bragin et al. 2004). HFO ripples have a broad source area, further suggesting that HFO arise from network oscillators. This, combined with the high variability of HFO events over time has led to interest in possible patterns in both spatial and temporal occurrence of HFO, possibly linked

![Figure 4.8 – Dunn Index (mean±S.D.)](image-url)
to changes in underlying epileptogenic activity. Rapid changes in HFO rate in a given area support the idea that HFO generation is driven by a nonstationary process with wide spatial distribution (Frauscher et al. 2017; J. Jacobs et al. 2012). Some investigations have been made of this possibility. Studies of HFO pattern in association with seizure generation have found links between the onset of specific seizure types and certain distributions of HFO occurrence (Lévesque et al. 2012; Salami et al. 2015), but have been limited to coarse estimates of pattern defined as raw changes in rate and only in association with seizure generation. One recent study looked at intermittent HFO sources as a link to SOZ during prolonged recordings (Gliske et al. 2018), but their analysis was also limited to rate over time.

The pattern identified in TLE SOZ by the PPM can be described as oscillation set of bursts, representing a 20-30 transient pattern of “burst-pause-burst.” A natural interpretation of such a pattern is a local circuit of activity leading to the initial pair HFO occurrence during an “up-state” followed a pause while activity travels through a larger regional circuit indicative of a network oscillator before entering “up-state” again with bursting HFO activity. The presence of a third wave “up-state” suggested by the smaller significance of the parameter representing the window 50-60s in the past implies that this looping network oscillation can reoccur, diminishing either over time or in response to compensatory mechanisms. Though speculative, this hypothesis is consistent with animal studies attempting to tease out the circuit mechanisms of seizure generation. First, the bursting pattern of HFO can be plausibly explained by the presence of not just synchronized bursting in the local microcircuit, but specifically repeated sets of rebound burst firing, leading to brief, 1-2 second pause between HFOs locally. This type of rebound burst firing has been implicated in seizure generation and epileptogenicity (Avanzini et al. 1993; Lee et al. 2014). A role for rebound bursting in seizure generation has been supported by recent optogenetic work as
well, demonstrating the optogenetic activation of interneurons in the epileptogenic zone was sufficient to produce interictal discharges and could promote seizure onset (Magloire et al. 2019). Larger network drivers have also been proposed, consistent with the larger 20-30 second pause observed in the detected motif. Feed-forward inhibition is theorized to be one the primary compensatory mechanisms in epilepsy (Pothmann et al. 2014) and a weakening or disruption of this process could allow seizure to propagate freely. Changes in this system have been shown to enable the transition to status epilepticus (Fan et al. 2017). Most strongly supportive of the idea that a recurrent process is involved in HFO and seizure generation are multiple studies finding a critical role for recurrent excitation in seizure generation (Wuarin and Dudek 2001; Zhang, Huguenard, and Buckmaster 2012). In these studies, it was found that larger, relatively slow networks of positive feedback and recurrent excitation led to seizure onset and susceptibility. Of particular interest in this case is that both studies found this effect in temporal lobe epilepsy, consistent with region in which the detected motif is found. Though still speculative without further work, it is possible the motif detected in this study by the point process model captures a complex interplay between local and regional microcircuits driven by disruptions in both excitatory and inhibitory processes.

A limitation in this study is the focus on ripple events, between 100-250 Hz, without considering “fast ripples” above 250Hz. Fast ripples have also been strongly linked to the SOZ and failure to consider them may lead to missing other relevant patterns that could be relevant to the area of focus. Additionally, the same caveats discussed in Chapter 3 regarding missed events due to the choice of detection method, filtering tools, and data sampling rate apply to this study as well. Further work on higher sampling rate data with particular emphasis on the behavior and pattern of fast ripples is advised.
Chapter 5: Investigation of Utility and Characteristics of Scalp HFO

5.1 Introduction
Scalp HFO’s have been investigated in the past few years as a noninvasive biomarker of epileptogenic activity but detection methods and analyses are lacking. In this aim, EEG data from a unique cohort of young epileptic patients from the CT Children Medical Center will be used to develop machine learning tools for the unsupervised detection of scalp HFO’s. In this chapter, a tool for detection of scalp HFO will be refined to a useable state, detected events will be validated against epileptologists’ assessment, and accuracy of putative events will be compared areas of clinical interest. Additionally, the relationship between HFO and asleep vs wakeful states will be investigated, and analysis of event phase will be performed.

5.2 Methods
5.2.1 Dataset
Novel investigation of scalp HFO required the collection of scalp EEG recordings from a pool of epilepsy patients. EEG recordings were collected from pediatric epilepsy patients in collaboration with Drs. Mark Schomer and Jennifer Madan-Cohen at the Connecticut Children’s Medical Center in Hartford, CT. Collection was conducted in accordance with CCMC IRB# 17-109. Data was collected between September 14, 2017 and September 13, 2018. 48 pediatric patients (age: 9.2 ± 5.3 y/o; 29 male, 19 female) were included in the study. Informed parental consent was given for all minors included in the study. For each patient, approximately 15 minutes of 10-20 configuration with bipolar montage scalp EEG recording was collected during sleep (15.6±3.3 min/ch) and during wakefulness (15.1±5.1 min/ch). Recordings were visually marked for interictal epileptiform discharges by Drs. Schomer and Madan-Cohen and the region of probable SOZ was assessed. Pediatric patients
were chosen as the target dataset for this initial investigation for several reasons. First, pediatric patients are an ideal subject group for the investigation of scalp HFOs, both because their less developed skulls produce less attenuation of the EEG signal and because it is highly desirable to replace invasive neurosurgeries, like iEEG implantation, with noninvasive methods in developing populations. Second, the dataset collected in collaboration with CCMC provides a diverse demography of the subject group, which increases the likelihood of reproducibility and generalizability of results. Third, CCMC was able to provide a dataset of higher than normal size for this study, reinforcing the validity and generalizability of any results.

5.2.2 Spike-ripple and Ripple Detection Algorithm

HFO spike-ripple detection was applied to each EEG recording in three stages as shown in Figure 5.1.

![Workflow for Spike-HFO and HFO Detection](image)
Spike-ripple occurrence was defined as the co-occurrence of a HFO ripple and an epileptiform spike event. First, automated scalp spike-ripple detection was performed according to a previously validated detector (Chu et al. 2017) with significant additional processing steps, applied to each channel independently. Briefly, raw scalp EEG recordings were band-pass filtered (170th order equiripple FIR filter, cutoff frequencies 100-300 Hz) and Morlet Wavelet transform was performed to acquire the analytic signal and compute the amplitude envelope. Candidate spike-ripples events were chosen as segments in which the amplitude envelope was greater than 85% values for the entire dataset for at least 20 ms. This pool of candidate spike-ripples was then automatically screened to remove false positives and artifacts. Candidates passed this stage of screening if they had: i) a minimum of 3 zero crossings to confirm oscillatory behavior and ii) a Fano factor less than 1 to ensure a non-random oscillation. The following clustering procedures was added to the workflow of the detector in (Chu et al. 2017). Second, a set of 10 features were computed for the remaining spike-ripple candidates. On raw EEG data, the line-length, SD, entropy, spectral peak, and gamma-beta power ratio were computed. On band-pass filtered signals, spectral centroid, energy, max peak ratio, max power ratio, and filtered entropy were computed. These 10 features were used as a feature vectors for unsupervised agglomerative clustering with cluster inclusion criteria defined according to Ward’s method,

\[ d_{ij} = d(\{X_i\}, \{X_j\}) = \|X_i - X_j\|^2, \]

Where \(d_{ij}\) is the minimized norm distance between nodes and \(X_i\) is the feature vector, with cluster number chosen by maximizing silhouette value to remove remaining artifacts and give 1st pass clustering candidates. Third, clustering based on waveform morphology correlation was performed. A low-pass interpolating filter was applied to each spike-ripple event remaining after
1st pass clustering to compensate for variability in event duration. The correlation between each spike-ripple waveform was computed and iterated Louvain clustering was applied to the resulting matrix of correlation coefficients. For each cluster, the average waveform was used as a template for later confirmation as a true event by inspection by clinicians. Additionally, the waveform clustering procedure was repeated on the rejected artifacts from the 1st pass clustering to verify that those candidate spike-ripples rejected by 1st pass clustering were morphologically distinct from true HFO events. A selection of sample spike-ripples were assessed by board-certified epileptologists.

Additionally, due the significant clinical relevance of ripple events distinct from those co-occurring with spikes, a detection algorithm was applied to detect ripple events not co-occurring with epileptiform spikes. The two-stage clustering procedure described above was also applied to the resulting pool of candidate ripples. A selection of these ripple events were also assessed by board-certified epileptologists to verify their accuracy.

5.2.3 Correlation of Spike-ripple and Ripple Events with Clinical Interictal Spikes

Because precise localization of the SOZ is not the goal of research in scalp HFO recording, HFO rate is a sufficient metric for assessment of the method. For each scalp EEG channel and recording, the HFO rate was computed as the average number of HFO events per minute, for both spike-ripple and ripple events. Rate of occurrence for detected spike-ripples and ripples was compared with channels in which epileptologists marked interictal spiking activity. Channels containing interictal spiking activity were classified as potential seizure onset zone (SOZ) channels. The rate of spike-ripple and ripple occurrence per minute in each channel was computed and compared between SOZ and non-SOZ channels. We compared the rates across patients and channel groups via a two-way ANOVA test with Tukey’s post-hoc (P-value P < .01).
Analysis was also performed on the aggregated channels across patients to determine population trends.

5.2.4 HFO Phase Analysis

The association between low-frequency components of scalp EEG and HFO event occurrence was investigated. The raw EEG signal was band-pass filtered (3rd order Butterworth filter, cutoff frequencies 1-8 Hz) and the Hilbert transform was used to acquire the analytic signal and compute the instantaneous phase angle of the signal for each channel. For each HFO event, the instantaneous phase at which it initiated was recorded. For events from each patient individually, and for aggregated events from all patients, circular statistics were used to determine the phase preference of HFO events. The presence of a significant phase preference was determined using the Rayleigh $z$ test:

\[ z = nr^2 \]

where $n$ is the sample size and $r$ is the mean phase vector strength of the events. The significance of phase preference for each patient and the aggregated data was assessed using the Rayleigh test for non-uniformity, determined as difference from a uniform distribution as defined by:

\[ Z_{\infty}^2 = \frac{2}{n} \sum_{j=1}^{m} \left( \sum_{k=1}^{n} \cos(j\phi_k) \right)^2 + \left( \sum_{k=1}^{n} \sin(j\phi_k) \right)^2 \]

Furthermore, we used the Watson-Williams test to check for a significant difference in mean phase angle between awake and asleep patients. To determine if HFO occurring in spike-bearing channels were distinct or followed a different phase preference from those occurring in spike-free channels, we separated the channels for each population into two groups, spike-bearing and spike-free, and repeated the above analyses, and used the Watson-Williams test to
determine if there was a significant difference in mean phase angle. Assessment of phase preference was repeated for both spike-ripple and ripple events.

5.3 Results
5.3.1 Dataset
EEG recordings were collected from pediatric epilepsy patients in collaboration with Drs. Mark Schomer and Jennifer Madan-Cohen at the Connecticut Children’s Medical Center in Hartford, CT. A total of 48 pediatric patients were included in the study of mix of ages and sex (age: 9.2 ± 5.3 y/o; 21 male, 15 female). For each patient, approximately 15 minutes of 10-20 configuration scalp with bipolar montage EEG recording was collected during sleep and during wakefulness. Recordings were visually marked for interictal epileptiform discharges by Drs. Schomer and Madan-Cohen and the region of probable SOZ was assessed.

5.3.2 Event Detection and Clinical Correlation
Spike-ripple detection was performed independently on each patient. A total of 7894 candidate spike-ripple events (1456 asleep; 5912 awake) were analyzed and 7077 (1293 asleep; 5784 awake) were considered possible HFO events after 1st pass clustering. Louvain correlation clustering further eliminated false positives, leaving 1859 (931 asleep; 928 awake) putative spike-ripple events for analysis. To confirm that Louvain correlation clustering did not remove true spike-ripples, Louvain clustering was repeated on events rejected during first round clustering. Figure 5.2 reports a subset of the waveform correlation matrix for Group 1 (1st pass accepted spike-ripples). Visual assessment confirmed the highest correlation post-clustering group as putative HFO and rejected all other groups.
Clinicians were able to identify interictal epileptiform discharges (IED), a marker of regions of clinical interest, in specific channels in 18 of 48 patients. In these cases, IED were marked by clinician inspection in 2.09±0.98 channels per patient (awake: 2.0±0.97; asleep: 2.18±1.01 [mean±SD]). In the asleep case, IED were marked in the channels with the highest spike-HFO rates in 18 of 18 patients. Furthermore, the average spike-HFO rate was significantly higher in IED-bearing channels than IED-free channels in 17 out of 18 asleep patients (paired t-test, P-value P<0.01), with a non-significant trend in an additional 1 out of 18 patients. In the awake case, the highest spike-ripple rate was detected in IED-bearing channels in 17 out of 18 patients. Additionally, the average spike-HFO rate was significantly higher in IED-bearing than IED-free channels in 16 out of 18 awake patients (paired t-test, P-value P<0.05), with a non-significant trend in an additional 2 out of 18 patients. Across patients, the spike-HFO rate was
significantly higher in IED-bearing channels than IED-free channels during sleep (paired $t$-test, $P$-value $P<0.02$) and wakefulness (paired $t$-test, $P$-value $P<0.05$). Finally, no significant HFO rate difference was reported between IED-free channels across the entire patient population. In the remaining 30 of 48 patients, generalized IED were observed by clinicians across multiple adjacent channels. In these cases, spike-HFO rates was aggregated across all channels, as the degree of generalization was often poorly defined and localized. Spike-HFO rates in IED-bearing channels of patients with channel-specific IED occurrence was significantly higher than the spike-HFO rate of patients with generalized IED during sleep (paired $t$-test, $P$-value $P<0.05$). Spike-HFO rates are reported in Figure 5.3.

The steps described above for spike-HFO detection were repeated for isolated HFO detection. HFO detection was performed independently on each patient. A total of 701442 candidate HFO events (211629 asleep; 489813 awake) were analyzed and 482395 (162839 asleep; 319556 awake) were considered possible HFO events after 1st pass clustering. Louvain correlation clustering further eliminated false positives, leaving 18297 (4755 asleep; 13542
awake) putative HFO events for analysis. In the asleep case, IED were marked in the channels with the highest HFO rates in 16 of 18 patients. Furthermore, the average HFO rate was significantly higher in IED-bearing channels than IED-free channels in 15 out of asleep 18 patients (paired $t$-test, $P$-value $P<0.05$), with a non-significant trend in an additional 2 out of 18 patients. In the awake case, the highest HFO rate was detected in IED-bearing channels in 14 out of 18 patients. Additionally, the average HFO rate was significantly higher in spike-bearing than spike-free channels in 12 out of 18 awake patients (paired $t$-test, $P$-value $P<0.05$), with a non-significant trend in an additional 4 out of 18 patients. Across patients, the HFO rate was significantly higher in spike-bearing channels than spike-free channels during sleep (paired $t$-test, $P$-value $P<0.02$) and wakefulness (paired $t$-test, $P$-value $P<0.05$). No significant HFO rate difference was reported between IED-free channels across the entire patient population. HFO rates in IED-bearing channels of patients with channel-specific IED occurrence was significantly higher than the HFO rate of patients with generalized IED during sleep (paired $t$-test, $P$-value $P<0.03$). HFO rates are reported in Figure 5.4.

![Figure 5.4](image)

**Figure 5.4.** Average scalp HFO rates for channels showing IED, not showing IED, and with generalized IED activity, in sleep and wakefulness. Bars and vertical lines indicate average and standard error of mean (SEM) across patients.
5.3.3 HFO Phase Analysis

For each channel and patient, the instantaneous phase angle of the low frequency (1-8 Hz) was calculated and the phase angle at the initiation of each spike-HFO event was recorded.

For each patient, the mean phase angle and vector strength were calculated, and the Rayleigh z test was used to test for a significant phase preference. In the asleep case, the mean spike-HFO phase angle was 2.36±.069 [mean±SEM] with a vector strength of .53±.11[mean±SD]. 18 of 18 asleep patients showed a significant spike-HFO phase preference (Rayleigh z test, P-value P<2.8E-98). In the awake case, the mean spike-HFO phase angle was 2.45±.073[mean±SEM] with a vector strength of .46±.10[mean±SD]. Spike-HFO phase directionality is reported in Figure 5.5.

![Figure 5.5. Polar histogram of spike-HFO phase preference for .5-8 Hz](image)

18 of 18 awake patients showed a significant spike-HFO phase preference (Rayleigh z test, P-value P<1.7E-93) The population-level HFO phase distribution was tested for significant non-uniformity. Spike-HFO phase angle distribution was very significantly non-uniform in both
asleep (Rayleigh test for non-uniformity, \( P\)-value \( P<2.1\times10^{-304} \)) and awake populations (Rayleigh test for non-uniformity, \( P\)-value \( P<1.4\times10^{-265} \)), confirming a strong phase preference for HFO events occurring both during sleep and wakefulness. Comparison of preferred phase angle for asleep and awake patients found no significant difference (Watson-Williams test, \( P\)-value \( P=.38 \)).

The above analysis was repeated for isolated HFO events. For each channel and patient, the instantaneous phase angle of the low frequency (1-8 Hz) was calculated and the phase angle at the initiation of each HFO event was recorded. For each patient, the mean phase angle and vector strength were calculated, and the Rayleigh \( z \) test was used to test for a significant phase preference. In the asleep case, the mean HFO phase angle was \( 2.19\pm.13 \) [mean\( \pm \)SEM] with a vector strength of \( .42\pm.15 \) [mean\( \pm \)SD]. 18 of 18 asleep patients showed a significant HFO phase preference (Rayleigh \( z \) test, \( P\)-value \( P<1.7\times10^{-32} \)). In the awake case, the mean HFO phase angle was \( 2.20\pm.25 \) [mean\( \pm \)SEM] with a vector strength of \( .21\pm.16 \) [mean\( \pm \)SD]. 18 of 18 awake patients showed a significant HFO phase preference (Rayleigh \( z \) test, \( P\)-value \( P<3.9\times10^{-7} \)). Figure 5 reports the polar histogram of HFO instantaneous phases and the mean phase angle and magnitude across aggregated asleep and awake patients, for IED-bearing, IED-free, and generalized IED channels. The population-level HFO phase distribution was tested for significant non-uniformity. HFO phase angle distribution was very significantly non-uniform in both asleep (Rayleigh test for non-uniformity, \( P\)-value \( P<1.1\times10^{-95} \)) and awake populations (Rayleigh test for non-uniformity, \( P\)-value \( P<1.3\times10^{-56} \)), confirming a strong phase preference for HFO events occurring both during sleep and wakefulness. Comparison of preferred phase angle
for asleep and awake patients found no significant difference (Watson-Williams test, \( P \)-value \( P = .14 \)). Figure 5.6 reports HFO phase directionality.

![Figure 5.6. Polar histogram of HFO phase preference for .5-8 Hz](image)

### 5.4 Discussion

In this chapter, the feasibility of detecting scalp HFO in an automated way was tested by development/refinement of an automated scalp HFO detection system. The system worked by identifying a large pool of possible HFO event, defined using characteristics typically used for detection of intracranial HFO. This produced an exceptionally large pool of possible events with a high false positive rate. In order to increase the specificity of the detector, events were eliminated from consideration using to steps of clustering removal. First, a set of 10 features were chosen on both raw and high-pass filtered signal that would do a good job discriminating between HFO, noise, and artifacts. Features based on spectral characteristics were chosen to isolate probable motion artifacts from the pool of probable events, based on the idea that motion
artifact tends to contaminate a broad range of spectral frequencies, whereas true HFO are isolated to high frequency components. Other features, such as entropy, work to discriminate true HFO from noise and background signal. This is particularly important when trying to detect scalp HFO due to the very low amplitude of HFO events after attenuation by the skull.

The second round of clustering was performed using the Louvain method on the waveforms of the remaining pool of events. Examination of these events showed that by chance a number of events have similar analytic and spectral characteristics to true HFO, but have differences in waveform and would appear visually dissimilar and not be regarded as true HFO by an experienced epileptologist. Events in this category were particularly common when HFOs alone were examined. Waveform clustering generated one cluster of true HFOs, as determined by visual inspection and consultation with a trained epileptologist, and several additional clusters of with similar, but non-relevant waveforms. These elimination steps reduced the number of detected spike-HFO events on scalp EEG to levels consistent with rates of detection on similar dataset of intracranial EEG, suggesting that detection accuracy has advanced to the point comparable to those studies. Furthermore, when the full detection system was applied, agreement between channels with the highest HFO rates and the channels identified as channels of interest by clinicians were near perfect, with 100% agree at the level of hemisphere lateralization.

Currently, the system for detection of HFOs alone is still likely oversensitive, with the number of events detected higher than HFO rates reported from intracranial EEG. However, those channels with the highest rates of HFO alone consistently match with the hemisphere of lateralization. While there is room for improvement, this is a promising first step. Additionally, while co-occurrence with spikes is still a helpful limiting factor for HFO detection, literature on
the diagnostic utility of co-occurring spikes and HFOs suggests that even with this limitation, the system can be useful.

The finding of a very strong phase preference of HFO events is an intriguing one, congruous with previous findings of phase amplitude coupling in interictal epileptiform discharges (Selvitelli et al. 2010; Amiri, Frauscher, and Gotman 2016). This is also in line with frequency band specific slowing as a marker of seizure generation (Lundstrom et al. 2019). Taken together, these results suggest that frequency and phase-specific processes may be critical to seizure generation. Further refinement of the detection procedure and additional analysis are needed to fully explore this relationship and the link between phase, HFO, and seizure onset.
Chapter 6: Conclusion

The goal of this dissertation was to achieve three aims: assessment the potential diagnostic utility of HFO in clinical drug resistant epilepsy by development of a tool based on HFO, identification and characterization of a temporal pattern of HFO occurrence, and development of a tool for detection of scalp HFO. Throughout the preceding 5 chapters, a foundation for this work was assembled and completion of these aims was achieved. In this final chapter, summary and conclusions based on these findings will be presented and possible useful future directions for this work will be discussed.

6.1 Diagnostic Utility of HFO

In chapter 3, an automated classification system was developed to provide patient- and patient-state-independent labeling of iEEG channels as SOZ or non-SOZ for SOZ localization as part as a clinical decision support system for the planning of epilepsy surgery. The successful development of that tool was taken as proof of the utility of HFO for this purpose. The system detects ripple events in multi-channel iEEG time series and determines the channel most likely to be SOZ-related by combining a machine learning feature nonlinear transformation of channel HFO rate rankings incorporating a consensus policy and SVM classification. The system was tested on over 2,400 hours of continuous multi-channel recordings from fourteen patients with various combinations of disease etiology, seizure onset zones, and electrode configurations. In its final form, the system was able to accurately identify the resected volume in patients with successful post-surgery outcomes (Class I) using only 30 minutes of iEEG data and no additional details or features. The system’s performance was consistent across the entire population of Class I patients and worked consistently regardless of changes in patient status, time of day, or
wake/sleep condition. Average performance values of sensitivity, accuracy, and area under the ROC curve were all above 0.90, which corresponds to less than one channel average difference between the predicted and resected volumes.

The system was compared to two alternative algorithms in order to demonstrate the relative contributions of the system components (nonlinear transformation and optimized SVM). Simple logistic regression combined with susceptibility index feature provides significant improvement that, when combined with SVM classification produces a system with high precision, reliability, and robustness for the identification of the SOZ. This work successfully demonstrates the utility of HFO for use in SOZ localization in the clinical setting. Additionally, the efficacy of a rank-based feature supports the theory in the field that HFO rates do tend to be highest in SOZ, even if the rate has too much variability to be applied practically.

6.2 Temporal Pattern of HFO

In chapter 4, point process modeling was used to detect and characterize a previously unknown pattern to HFO occurrence. It was shown that in the SOZ of TLE patients such a pattern exists, following a motif of HFO burst firing with 20-30 pauses in between. This pattern was not found outside the SOZ in TLE patients, and was also not found in any channels in subjects with focal areas in the frontal and parietal lobes.

The extent to which this pattern was meaningfully specific to the SOZ in TLE patients was assessed using methods used determine cluster quality. By treating the point process model parameter vector of each channel as a point in parameter space and using 2 fixed clusters set according to known groups of interest (SOZ vs non-SOZ), multiple measures of cluster quality and separability were applied. It was shown that the parameters describing the motif found in TLE SOZ channels was highly consistent across SOZ channels and provided clear separation from non-SOZ channels. No such separation was achieved in NTLE patients and no separation was achieved.
when using HFO rate vectors in this way. Thus, it can be concluded that the pattern detected by the PPM does better job discriminating SOZ than HFO rate.

Efforts were made to theorize a physiological basis for the detected pattern in TLE SOZ. The pattern consists of a “burst-pause-burst”, suggesting a mix of local and network circuit activity. This idea is consistent with animal studies of circuit mechanisms of seizure generation. Rebound burst firing has been shown to be relevant to this phenomena (Avanzini et al. 1993; Lee et al. 2014) and further optogenetic work implicates interneurons in the epileptogenic zone in interictal discharges and seizure onset (Magloire et al. 2019). Larger network drivers have also been proposed, consistent with the larger 20-30 second pause observed in the detected motif. A process of recurrent excitation in seizure generation has been found in multiple studies (Wuarin and Dudek 2001; Zhang, Huguenard, and Buckmaster 2012), supporting the interpretation of slow networks of positive feedback and recurrent excitation in temporal lobe epilepsy, consistent with region in which the detected motif is found. Confirmation of this complex system of local and regional microcircuits is speculative and beyond the scope of this work, but provides a potential direction for further investigation of this pattern and general patterns in HFO to pursue.

6.3 Detection and characterization of scalp HFO

In chapter 5, the possibility of accurate and useful detection of scalp HFO by an automated detector was investigated by the development of such a detector and assessment of its performance in collaboration with trained epileptologists at CCMC. The system starts by identifying a large pool of potential HFO events. This first wave of event identification used metrics common to the detectors already developed for use on intracranial EEG recordings, including line length, max amplitude, and zero crossings. Because of the difficulties added to this process by attempting to detect events after attenuation of the high frequency elements of the signal by the skull, the detector at this point must be vastly oversensitive with a high false
positive rate. In order to increase the specificity of the detector, events were eliminated from consideration using two steps of clustering removal. The first round of clustering removal was performed using features selected on raw and high-pass filtered signal, with the idea that spectral characteristics would do a good job highlighting probable motion artifacts based on the idea that motion artifact tends to contaminate a broad range of spectral frequencies, and entropy would discriminate true HFO from noise and background signal. This first set of clustering removal was fairly successful, but upon visual inspection of remaining putative HFOs, examples were found that visually were clearly not true HFO, but had spectral characteristics and amplitudes consistent with HFO, leading to them being grouped with the putative true HFO. To catch these events, a second round of clustering removal was performed using the Louvain method on the waveforms of the remaining pool of events. Waveform clustering generated one cluster of true HFOs, as determined by visual inspection and consultation with a trained epileptologist, and several additional clusters of with no-relevant waveforms. After these additional false positive removal steps, the number of detected spike-HFO events on scalp EEG was consistent with the rates of detection on similar datasets of intracranial EEG. At this point in analysis, confidence in the accuracy of detection was supported by agreement between channels with the high putative HFO rates and the channels identified as channels of interest by clinicians and 100% agreement at the level of hemisphere lateralization.

The detection pipeline was also applied to the detection of just HFOs. Even with the multiple steps of false positive removal, it is still likely oversensitive, with the number of events detected implausibly high. Despite this, channels with the highest rates of HFO alone consistently match with the hemisphere of lateralization, which shows positive indications of accuracy.
Phase preference of HFO events is an interesting finding, theoretically in line with previous work showing phase and frequency traits in other markers of epilepsy like IED and ictal slowing. This may indicate a link between frequency/phase-specific processes and seizure generation.

6.4 Future Work

The work presented in chapter 3 represents a significant improvement over the current state of the art in seizure onset zone localization. However, further refinements are always possible and maximizing results can only benefit patients and clinicians. The most pressing future direction for this work though is completion of the steps necessary to allow this system, or an improved form of it, to enter actual clinical usage where it can be of direct benefit to doctors and patients. This will likely require a multi-center study, with both prospective and retrospective features before this level of implementation becomes viable.

The pattern detected in TLE SOZ in chapter 4 raises interesting questions for future research directions. High quality molecular and electrophysiological neuroscience work will be needed to parse out and confirm the underlying physiological causes of the detected pattern and HFO. More directly related to the methods in this work, the failure to find a pattern of HFO occurrence outside the temporal lobe raises further questions. It is worth investigating if other methods of pattern detection can identify a different but equally stable motif in epilepsies with focal areas in frontal or parietal lobe. And if it is confirmed that there is no pattern to these events, work to understand why promises to deliver fascinating results.

The scalp HFO detection system from chapter 5 presents some of the exciting and potentially fruitful possibilities for additional work. First, there remains work to be done in improving the performance of the detector, especially when attempting to identify HFOs in the absence of spikes. Improvement in this area will likely require the selection of new features and
the addition of further steps of false positive rejection. More broadly, the success of the detector to identify scalp HFO in general opens the door to a variety of HFO-centric epilepsy research paths, both in terms of further characterizing this promising biomarker and its relationship with seizure generation and SOZ, and in terms of applications for HFO beyond SOZ localization. One promising avenue of research is early screening of anti-epileptic drug screening and estimation of disease severity from HFO. These projects were not feasible to pursue when invasively collected HFO were the only option, but offer exciting ways to put noninvasively collected HFOs to work.
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