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Beatriz Martinho Cardoso da Silva

Epilepsy Seizure Prediction Based on HRV Analysis

Thesis submitted to the Faculty of Science and Technology of the University of Coimbra for the degree of Master in Biomedical Engineering with specialization in Clinical Informatics and Bioinformatics, supervised by Prof. Dr. César Alexandre Domingues Teixeira and MSc Adriana Costa Leal.

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Resumo

Estima-se que, para cerca de um-terço dos pacientes com epilepsia que tomam fármacos anti-epiléticos, estes não previnam crises. Deste modo, a previsão de crises surge como uma potencial solução para mitigar o fardo da epilepsia para estes doentes e cuidadores.

Os modelos de previsão de crises dependem fortemente de conhecimento relativo a percursores pré-crise e, portanto, da caracterização apropriada do intervalo pré-ictal. A abordagem padrão do estado-da-arte para a definição do pré-ictal consiste na realização de uma *grid-search* discreta numa gama de intervalos seguida da escolha daquele que leva à melhor performance de previsão. No entanto, esta abordagem é subótima devido à incapacidade de abordar a heterogeneidade do processo de geração de crises. Por conseguinte, foi recentemente proposta a aplicação de métodos de aprendizagem não supervisionada (mais especificamente, técnicas de *clustering*) para caracterizar com precisão o intervalo pré-ictal.

Tratando-se da fonte primária de informação neurológica, o Eletroencefalograma (EEG) tem sido amplamente utilizado em previsão de crises. Adicionalmente, entre outros biossinais, o Eletrocardiograma (ECG) tem sido extensivamente referido como uma importante fonte não cerebral de alterações pré-crise. Esta é uma alternativa atrativa dada a facilidade e conforto de aquisição deste sinal numa situação da vida real.

O presente estudo teve como objetivo o desenvolvimento de modelos de previsão de crises que integram informação sobre os intervalos pré-ictais obtida a partir de *clustering*. Comparámos a performance de modelos de previsão que incorporam *grid-search* do pré-ictal específica para cada crise reportada no estado-da-arte com modelos construídos utilizando informação de pré-ictal obtida com técnicas de *clustering*. Os modelos foram construídos utilizando características da Variabilidade do Ritmo Cardíaco extraídas de sinais ECG adquiridos durante a monitorização pré-cirúrgica num grupo de 41 pacientes com epilepsia do lobo temporal (armazenados

na base de dados EPILEPSIAE).

A análise da performance dos modelos em termos de sensibilidade e Taxa de Falsos Positivos por Hora (FPR/h) revelou diferenças estatisticamente significativas apenas para a FPR/h. Mais especificamente, em alguns casos, observámos FPR/h mais baixa quando utilizada a informação de intervalos pré-ictais identificada através de *clustering*. Ambas as abordagens revelaram performance insatisfatória, tendo sido obtida sensibilidade de 36.26 ± 41.76 %, FPR/h de 0.72 ± 1.53 h^{-1}, e performance superior ao acaso para 41.5 % dos doentes (utilizando informação obtida com *clustering*).

Em conclusão, apesar de a utilização de informação de *clustering* sobre atividade pré-ictal ter levado a melhorias nos resultados em alguns casos, são necessários mais estudos para inferir sobre as vantagens de utilizar informação de pré-ictal específica para cada crise obtida a partir de técnicas de *clustering* para desenvolver modelos de previsão de crises.

Palavras-chave: Epilepsia, Previsão de Crises, Eletrocardiograma, Intervalo pré-ictal

Abstract

It is estimated that, for about one-third of patients with epilepsy taking anti-epileptic drugs, these do not prevent seizures. Thus, seizure prediction arises as a potential solution to mitigate the burden of epilepsy on these patients and caretakers.

Seizure prediction models heavily rely on knowledge regarding pre-seizure precursors and, therefore, on the proper characterization of the preictal interval. The standard state-of-the-art approach for preictal definition consists in performing a discrete grid-search on a range of intervals and choosing the one leading to the best prediction performance. However, this approach is sub-optimal due to the inability to address the heterogeneity of the seizure generation processes. Thus, applying unsupervised learning methods (namely clustering techniques) to accurately characterize the preictal interval has been recently proposed.

As the main source of neurological information, the Electroencephalogram (EEG) has been widely used in seizure prediction. Additionally, among other biosignals, the Electrocardiogram (ECG) has been extensively referred as an important non-cerebral source of pre-seizure alterations. This is an attractive alternative due to the ease and comfort of acquisition of this signal in a real-life setting.

The present study aimed at developing seizure prediction models that integrate information about preictal intervals obtained from clustering. We compared the performance of prediction models integrating seizure-specific preictal grid-search with the models built using preictal clustering information. The models were built using Heart Rate Variability (HRV) features extracted from ECG signals acquired during pre-surgical monitoring in a group of 41 patients with temporal lobe epilepsy (stored in the EPILEPSIAE database).

Analysis of the model performance in terms of sensitivity and False Positive Rate per Hour (FPR/h) revealed statistically significant differences only for the FPR/h. Specifically, in some cases, we observed lower FPR/h when using information of the preictal intervals identified with clustering. Both approaches performed unsat-

isfactorily, with 36.26 ± 41.76 % sensitivity, 0.72 ± 1.53 h^{-1} FPR/h, and models performing above chance for 41.5 % of patients (when using information from clustering).

In conclusion, even though using information of preictal intervals obtained with unsupervised learning methods led to improved results in some patients, more studies are required to infer about the advantages of using seizure-specific preictal information obtained with unsupervised methods to develop seizure prediction models.

Keywords: Epilepsy, Seizure prediction, Electrocardiogram, Preictal interval

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List of Abbreviations

AED Anti-Epileptic Drug. 1, 2, 3, 9, 17, 25, 26, 27, 30, 40, 46
ANN Artificial Neural Network. 41, 84
ANS Autonomic Nervous System. xiv, xvii, xxi, 2, 4, 5, 24, 25, 26, 27, 28, 29, 30, 31, 34, 50, 80
AUC Area Under the Curve. xviii, xxii, xxiii, 18, 56, 57, 65, 66, 68, 69, 74, 75, 76, 77, 80, 81, 83, 87, 110, 111, 118, 119

BP Blood Pressure. 24, 25, 26

CSI Cardiac Sympathetic Index. 32, 34, 35, 41, 42, 43
CVI Cardiac Vagal Index. 32, 34, 42, 43

DBSCAN Density-Based Spatial Clustering of Applications with Noise. 35
DFA Detrended Flunctuation Analysis. 32, 34, 35, 53, 123, 124, 125, 126, 127, 128
DRE Drug Resistant Epilepsy. xiii, 1, 2, 9, 17, 26, 28, 29, 35, 36, 39, 41, 42, 43, 44, 50, 90

ECG Electrocardiogram. xiv, xvii, xviii, 2, 4, 5, 18, 22, 23, 28, 34, 39, 40, 48, 50, 52, 75, 84, 85, 89, 90
EEG Electroencephalogram. xv, xxii, 2, 7, 8, 9, 10, 14, 18, 39, 40, 45, 50, 65, 80, 83, 84, 85, 89, 90

FBTC Focal to Bilateral Tonic-Clonic. 8, 27, 28, 41, 51
FN False Negative. 15, 17
FOA Focal Onset Aware. 51, 85, 86, 87
FOIA Focal Onset Impaired Awareness. 41, 51, 85, 86, 87
FP False Positive. 12, 13, 15, 16, 17, 19
FPR/h False Positive Rate per Hour. xvii, xviii, 3, 12, 14, 15, 16, 17, 18, 19, 40, 41, 42, 43, 45, 49, 61, 62, 66, 67, 69, 71, 73, 74, 75, 81, 82, 83, 84, 85, 86, 87, 89, 114, 115, 116, 117, 118, 119, 120, 121

HR Heart Rate. xiv, 23, 24, 25, 26, 27, 28, 40

HRV Heart Rate Variability. xiv, xv, xvii, xxi, xxii, 4, 23, 24, 25, 29, 30, 31, 32, 34, 35, 36, 37, 40, 41, 42, 43, 44, 47, 48, 52, 53, 65, 80, 81, 84, 89, 90, 124, 125, 127

IBE International Bureau for Epilepsy. 5
ILAE International League Against Epilepsy. xvii, 5, 6, 7, 9
IT Intervention Time. 12

MRI Magnetic Resonance Imaging. 1
mRMR minimum Redundance Maximum Relevance. 43, 57

ROC Receiver Operating Characteristic. xvii, 17, 60, 61
RQA Recurrence Quantification Analysis. 32, 33, 34, 35, 43, 53, 123, 124, 125, 126, 127
RRI R-R Interval. xviii, xix, xxiii, 23, 24, 30, 32, 41, 42, 43, 52, 65, 122, 123, 124, 125, 126, 127, 128

SOP Seizure Occurrence Period. xvii, 2, 3, 11, 12, 13, 14, 16, 18, 19, 41, 44, 48, 67, 80, 81, 82, 83, 84
SPH Seizure Prediction Horizon. xvii, 2, 3, 11, 12, 13, 14, 16, 18, 19, 41, 44, 48, 54, 60, 67, 69, 76, 80, 81, 82, 84
SUDEP Sudden Unexpected Death in Epilepsy. 10, 26, 27, 28, 29, 30
SVM Support Vector Machines. 41, 42, 43, 45, 58, 59, 60, 65, 82, 84, 106, 107, 108, 109, 110, 111, 112, 113

TLE Temporal Lobe Epilepsy. 3, 9, 27, 28, 29, 35, 40, 42, 43, 44, 50, 80, 81, 82, 83, 84
TN True Negative. 15
TP True Positive. 12, 13, 15, 16

1

Introduction

In this Chapter we present the motivation for this study in Section 1.1, as well as the context of the problem in Section 1.2. The expected goals and contributions are described in Section 1.3. Lastly, the outline of the document can be found in Section 1.4.

1.1 Motivation

Epilepsy is one of the most common neurological diseases in the world, affecting about 1% of the world's population [1]. Currently, it is estimated that one-third of patients with epilepsy suffer from Drug Resistant Epilepsy (DRE), characterized by the lack of response to Anti-Epileptic Drugs (AEDs) [2]. Less than 1% of these are admitted into epilepsy centres to evaluate the possibility of undergoing surgery [3, 4]. This evaluation considers clinical information such as Magnetic Resonance Imaging (MRI) studies and knowledge of the seizure focus [5], thus, at the end, not all patients qualify for surgery. Additionally, although surgery is reported to result in seizure freedom in 58% to 70% of the DRE cases [6, 7], its high cost and risk of adverse cognitive consequences may present significant barriers to the wider consideration of this treatment [3].

DRE represents a considerable burden for the patients, as well as their families and caregivers [8]. The unpredictability of seizures can be highly limiting, presenting a significant risk of trauma and injuries [8–10]. Additionally, the stigma and discrimination associated with the disease can cause mental health issues such as anxiety and depression [11, 12]. The patients' capacity to lead a normal life is severely hindered. Many refrain from certain daily activities such as leaving the house or driving, and report low levels of productivity at work. Furthermore, there is a considerable monetary burden associated with the disease, for both the patients and healthcare systems [11].

Finally, evidence of a preictal state has been reported in the literature. This in-

terval corresponds to the transition between the normal (interictal) and the seizure (ictal) brain state [13]. This fact prompts the development of seizure prediction systems as a potentially relevant solution to improve the quality of life of DRE patients. Moreover, seizure prediction may even prove useful for patients with epilepsy not suffering from DRE, for whom long-term treatment with AED can be the cause of neurological side effects. Thus, these patients could benefit from on-demand administration of rescue medication instead of continuous AED intake [10, 14].

1.2 Context

Based on the fact that epilepsy is a neurological disease, the Electroencephalogram (EEG) is widely used in epilepsy diagnosis and during pre-surgical monitoring of DRE patients [15, 16]. Furthermore, since the advent of seizure prediction studies in the 1970s, the EEG has also been the primary source of information in the field.

In addition, several studies have demonstrated that epileptic seizures can cause alterations in Autonomic Nervous System (ANS) control, either inhibiting or activating the sympathetic and parasympathetic systems. This, in turn, may cause changes in the normal functioning of the physiological systems under their influence, including the cardio-respiratory function [13, 17]. Such evidence prompted research studies to report the feasibility of using Electrocardiogram (ECG) signals in seizure prediction systems. Compared to the EEG, the acquisition of the ECG signal is easier, less costly, and more comfortable. Nowadays, ECG signal acquisition can even be done using wearables such as smartwatches [18–20].

The development of such seizure prediction models entails real-time data acquisition, pre-processing and classification. When a seizure is predicted, an alarm is raised and one alternative is warning the patient in order to avoid potentially dangerous activities, for instance, driving or swimming. Another option could be to integrate these algorithms into closed-loop systems, which deliver rescue medications or electrical stimulation to stop seizure progression [2, 10, 21]. The raised alarm must be associated with an interval that allows the patient to take action, the Seizure Prediction Horizon (SPH), as well as the period within which the onset of the seizure is expected, the Seizure Occurrence Period (SOP).

The preictal period constitutes an important aspect of seizure prediction studies, which heavily depend on its correct identification. However, the determination of preictal localization is a matter of active discussion among researchers. The literature on the topic provides evidence of its existence [13], but a consensus has not yet been reached when it comes to its localization. Moreover, it has been reported

that the preictal interval varies not only between patients, but also between seizures within the same patient [2]. Currently, the state-of-the-art approach for the determination of the preictal period is based on a grid-search, where a range of intervals are tested and the interval yielding the best performance is chosen as the optimal value. However, besides being imprecise and computationally expensive, this method offers little insight into the mechanisms of seizure generation.

Thus, with the aim of providing an alternative approach to the determination of the localization of the preictal period, Leal et al. [22] developed a study based on unsupervised learning using a dataset composed of 41 Temporal Lobe Epilepsy (TLE) patients from the EPILEPSIAE database [1, 16]. By applying clustering algorithms to combinations of three features, in a seizure-specific manner, it was possible to identify and quantify the preictal period for 41% of the seizures analyzed. If this method is accurate in identifying the preictal, it will provide added value to seizure prediction methodologies by producing more accurate target inputs for training. Hereupon, it is necessary to validate the results obtained in that study. This entails the incorporation of the estimated preictal times into a seizure prediction model and the evaluation of their impact on the performance when compared to the standard state-of-the-art approach described above.

Besides the difficulties added by lack of knowledge regarding the seizure generating processes and the preictal period, most seizure prediction studies present shortcomings which limit their real-world applicability. Firstly, the use of low-quality databases, containing discontinuous, short-term recordings and low number of patients and seizures [23, 24]. Secondly, the fact that seizure prediction models are developed without considering inter-patient variability and confounding patterns such as concept drifts. The latter include, for example, circadian rhythms or oscillations in brain activity resulting from changes in AED administration [2].

The results of seizure prediction methodologies should be evaluated in light of the performance metrics, sensitivity and False Positive Rate per Hour (FPR/h), in order to enable the comparison between studies. The effects of parameters such as the SOP and SPH on the patient's daily life should also be carefully evaluated. For instance, long durations may increase stress and anxiety unnecessarily [25]. Lastly, statistical validation is essential in order to ensure that the developed algorithms perform above chance levels. Although the relevance of this step has been systematically stressed out in the literature, few studies have considered it in their analysis.

1.3 Research Goals

The main goal of this thesis is to assess the impact of using preictal information (previously obtained using clustering methods) in the performance of seizure prediction models. The major expected contributions of this research project are the following:

- Development of patient-specific supervised learning models for seizure prediction using cardiovascular information, more specifically Heart Rate Variability (HRV) features extracted from the ECG.
- Evaluation of the impact of integrating information regarding the preictal interval starting time (obtained from clustering) into a seizure prediction model. This entails the comparison to the traditional grid-search approach, as well as proper statistical validation to ensure that the algorithm outperforms a random predictor.

1.4 Outline

This document is composed of five additional chapters, structured as follows.

Chapter 2 presents relevant background information on the topics of epilepsy, epileptic seizure prediction, the ECG signal, the Autonomic Nervous System, and changes in the cardiovascular system related to seizures.

Chapter 3 is related to the state of the art in seizure prediction, particularly ECG-based methodologies.

Chapter 4 describes the adopted methodology.

Chapter 5 reports the results obtained, as well as their discussion and comparison to those reported in seizure prediction studies in the literature.

Chapter 6 presents the main conclusions and future work.

2

Background Concepts

This Chapter introduces the background concepts necessary to understand the present document. Firstly, in Section 2.1, concepts related to epilepsy and its clinical classification are discussed. In Section 2.2, the main seizure prediction concepts are presented. In Section 2.3 a brief description of the Electrocardiogram signal is provided. In Section 2.4, the main functions of the Autonomic Nervous System and its relation to the cardiovascular system are discussed. Finally, Section 2.5 presents an overview of the main changes in different cardiovascular parameters related to epileptic seizures.

2.1 Epilepsy and Epileptic Seizures

Epilepsy is one of the most common neurological disorders in the world, secondly to stroke [10], and is estimated to affect about 1% of the world's population [1]. It is a chronic disease characterized by the recurrent occurrence of seizures, which are caused by abnormal synchronization of neuronal activity in the brain [11, 26].

In 2005, the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) reached a consensus about the definitions of epilepsy and epileptic seizures [26]:

*"An **epileptic seizure** is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain."*

*"**Epilepsy** is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure."*

Later, in 2014, the ILAE proposed a practical clinical definition of epilepsy, where it is characterized by one of the following conditions [12]:

1. *"At least two unprovoked (or reflex) seizures occurring > 24 h apart."*
2. *"One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years."*
3. *"Diagnosis of an epilepsy syndrome."*

Finally, the ILAE also updated the classification framework of the epilepsies (see Figure 2.1). According to this new scheme, the diagnosis of epilepsy can be performed at three levels - **seizure type**, **epilepsy type**, and **epilepsy syndrome**, enabling different levels of classification when different resources are available to the clinician [27]. Over the next subsections, these three levels will be explored in deeper detail.

Herein, co-morbidities and etiology will not be further discussed, although the latter may be an important aspect to take into account in treatment selection, for instance. However, it should be noted that the high clinical heterogeneity of disease is, initially, a result of the high variety of etiological causes, the most common being infectious etiology. The remaining etiologic groups are structural, genetic, metabolic, immune and unknown (see Figure 2.1) [27].

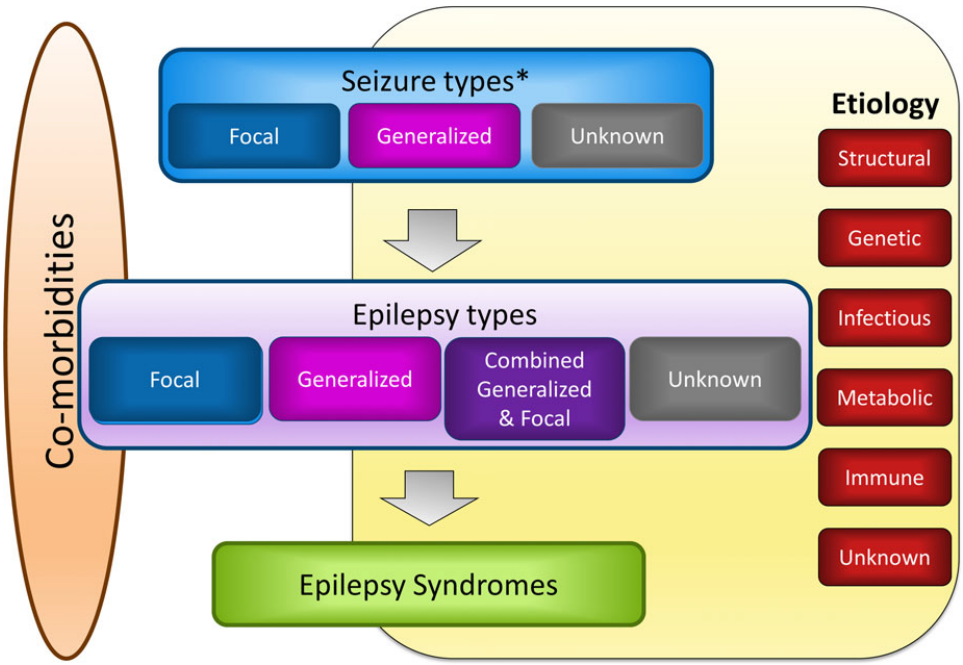


Figure 2.1: ILAE framework for classification of the epilepsies. *Denotes onset of seizure. Source: Scheffer et al. 2017 [27]

2.1.1 Seizure Type

The first level of the diagnosis of epilepsy is the classification of the seizure type. Fisher et al. [28] recently proposed an operational classification of seizure types, depicted in Figure 2.2. It should be noted that the classification scheme in Figure 2.2 is not hierarchical, which means that if there is not sufficient available information to group the seizure into a category in any of the levels present, it might be skipped [28].

The classification of the type of seizure begins with the identification of the place of onset in the brain, either **focal**, **generalized**, or **unknown**. If there is not enough information, the seizure is said to be **unclassified** [28]. This classification is performed by analyzing the video-EEG and imaging studies [27].

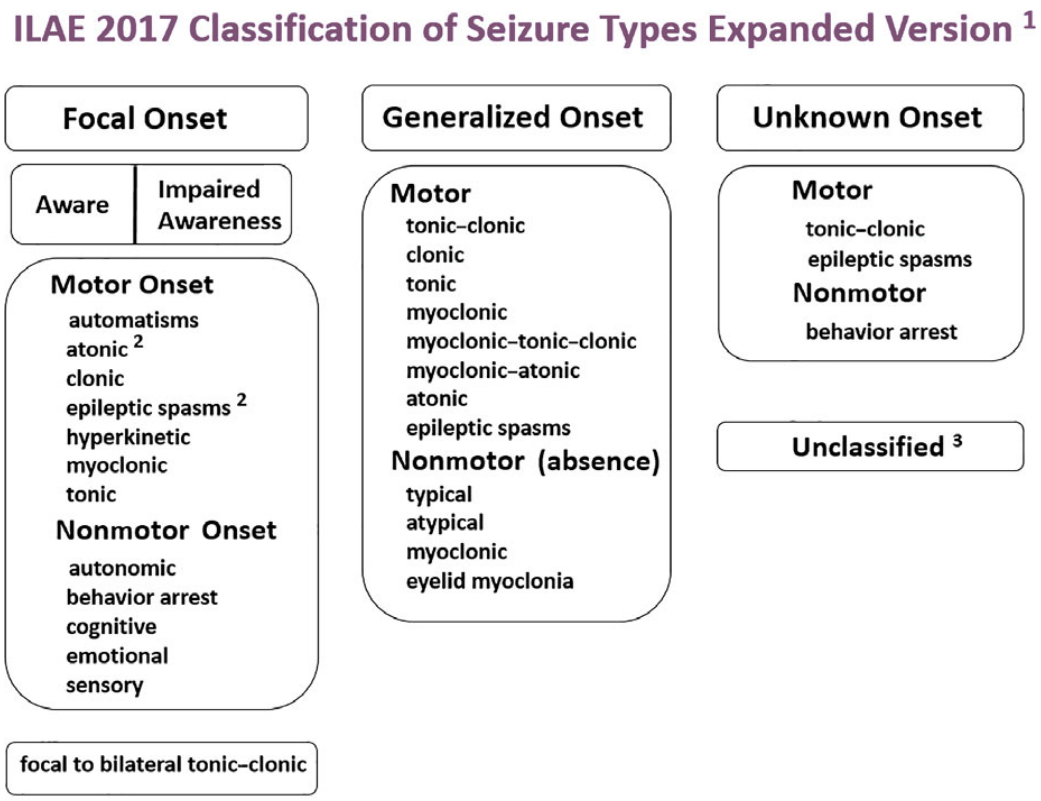


Figure 2.2: Expanded ILAE 2017 operational classification of seizure types. [1]Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms. [2]Degree of awareness usually is not specified. [3]Due to inadequate information or inability to place in other categories. Source: Fisher et al. 2017 [28]

Focal Seizures

In the case of focal onset seizures, characterized by starting on one side of the brain, the level of awareness of the patient (**aware** or **impaired awareness**) might

be included in the classification. Additionally, seizures may be grouped according to the occurrence of motor and non-motor symptoms (**motor onset** and **nonmotor onset**), and the most prominent of these symptoms might be added to provide further information (see options in Figure 2.2).

Generalized Seizures

Generalized seizures engage both sides of the brain, and can also be subdivided into **motor** and **non-motor** (absence) seizures, with the addition of the most prominent symptom.

Unknown Seizures

In some cases, it is not possible to determine the focus of the seizure, and it is deemed unknown. In this case, the terms **motor** and **non-motor** might also be used, and further descriptors of the symptoms from the list may also be added.

Focal to Bilateral Tonic-Clonic

Focal to Bilateral Tonic-Clonic (FBTC) is a special type of seizure reflecting a specific propagation pattern in the brain, which starts within one hemisphere and propagates to the other.

2.1.2 Epilepsy Type

The second level of the diagnosis of epilepsy is the epilepsy type. The classification of epilepsy type constitutes a division into **Focal**, **Generalized**, **Combined Generalized and Focal**, and **Unknown** Epilepsies (see Figure 2.1) [27].

Focal Epilepsy

Focal Epilepsies occur when the EEG presents interictal focal epileptiform discharges, and include focal aware seizures, focal impaired awareness seizures, focal non-motor seizures, and FBTC seizures.

Generalized Epilepsy

A patient is diagnosed with Generalized Epilepsy if the EEG shows interictal generalized spike-wave activity. This classification includes absence, myoclonic, atonic, tonic and tonic-clonic seizures.

Combined Generalized and Focal Epilepsy

Combined Generalized and Focal Epilepsies refer to patients who experience both generalized and focal seizures. Thus, the EEG might show both focal epileptiform discharges and spike-wave activity.

Unknown Epilepsy

When the patient has been diagnosed with epilepsy but there is no sufficient information available to determine the epilepsy type, the term Unknown is applied.

2.1.3 Epilepsy Syndrome

The third level of the epilepsy diagnosis consists of the epilepsy syndrome classification. The epilepsy syndrome can be identified by resorting to information regarding seizure types, EEG, imaging data, and other clinical information. Epilepsy syndromes may be associated with etiology and thus carry treatment implications. It is important to refer that there is no formal classification of syndromes by the ILAE [27].

Temporal Lobe Epilepsy (TLE) is the most common type of focal epilepsy, affecting about 60% of these patients. TLE usually begins during childhood or teenage years and is characterized by the occurrence of seizures involving the temporal lobes [29, 30]. TLE includes both focal aware seizures and focal impaired awareness seizures [29]. Patients suffering from TLE usually do not become seizure-free with AEDs alone, although they may help decrease the number of seizures. In such cases, surgery is considered an option to control seizure occurrence [29]. Another alternative to increase quality of life is seizure prediction.

2.1.4 Drug Resistant Epilepsy (DRE)

Drug Resistant Epilepsy may also be referred to as medically refractory, intractable, or pharmacoresistant epilepsy [31]. The following definition has been proposed by the ILAE Task Force on Therapeutic Strategies [31] in 2009:

*"**Drug Resistant Epilepsy** may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."*

In the same report, seizure freedom was defined as *"freedom from all types of seizures for 12 months or three times the preintervention interseizure interval, whichever is longer".*

This condition affects about one-third of patients with epilepsy [2], and individuals suffering from it are at an increased risk of premature death, namely Sudden Unexpected Death in Epilepsy (SUDEP). Additionally, the unpredictability of seizures increases the probability of sustaining injuries, and psychological issues, this way reducing the patient's quality of life [32]. For this reason, these patients are the focus of seizure prediction methods, which can drastically improve their quality of life.

2.2 Seizure Prediction and Detection

2.2.1 Seizure Onset

The seizure onset refers to the start of the seizure. Two different onsets might be considered: clinical and electrographic. The clinical onset is the moment when the first clinical symptoms arise. The electrographic onset corresponds to the first visible EEG signs, usually some seconds before the clinical onset [33]. This should not be confused with the preictal period, which refers to changes occurring before the more evident and significant changes at the electrographic onset.

Since the determination of the clinical onset can sometimes be difficult and uncertain, it is usual to annotate the electrographic onset [33].

2.2.2 Early Seizure Detection

Early Seizure Detection corresponds to the detection of the electrographic onset, before the first clinical manifestations of the seizure arise. Although this approach is not suitable for warning systems due to its short anticipation time, it might be useful for timely targeted intervention by a closed-loop treatment delivery system, if the patient is not yet past the "point of no return", i.e., if the evolution into a seizure state can still be stopped [33]. Additionally, automated detection systems can also be helpful in (i) determining the source and dynamics of seizures (diagnosis), and (ii) evaluating the effect of a given treatment [34].

2.2.3 Seizure Prediction

Seizure prediction is the focal point of this thesis, and its aim is to develop technologies capable of anticipating the occurrence of seizures.

The brain dynamics of patients with epilepsy can be divided into four distinct periods: the interictal, preictal, ictal and postictal (see Figure 2.3). The interictal

can be simply described as a period of normal dynamics. The preictal period precedes a seizure. The seizure (*ictus*) is denominated the ictal period. The postictal is the interval after the seizure [35]. It should be noted that, despite this clear division, the location of these periods is still not clearly defined.

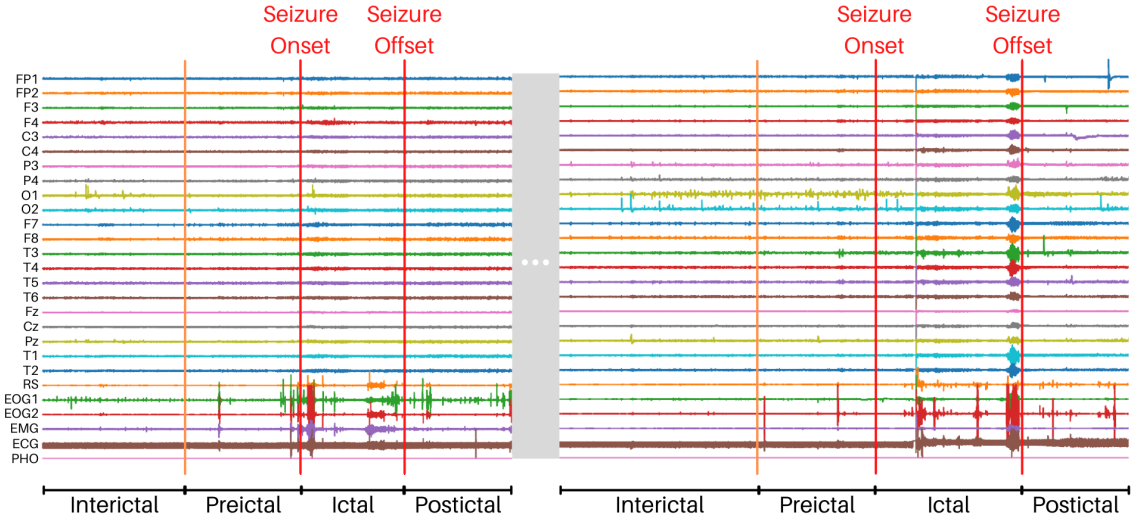


Figure 2.3: The four periods of a seizure episode represented on seizures 1 and 2 of patient 402: interictal, preictal, ictal and postictal. The example is merely illustrative, as there is no fixed localization defined for the preictal period. Adapted from: Cui et al. 2018 [35]

Therefore, seizure prediction aims at building systems capable of acquiring online data and applying algorithms in order to detect the preictal period. The prediction is usually associated with a Seizure Occurrence Period (SOP) and Seizure Prediction Horizon (SPH). The SOP is the time window during which the onset is expected to take place, and the SPH corresponds to the interval between the alarm and the SOP, during which preventive measures might be taken in anticipation of a seizure. From the point of view of the user, shorter SOPs are preferable, as this reduces the level of uncertainty in the prediction. Regarding SPH, longer periods are advantageous, since they provide more time to react to the alarm and prepare for the upcoming seizure [2, 33].

These seizure prediction methodologies might be integrated into warning systems, which warn the patient or caregivers of the eminence of a seizure and allow them sufficient intervention time to reduce the negative effects that might result from it. This may include avoiding potentially dangerous activities, such as driving or swimming, or taking medication. In addition, closed-loop systems might be developed that administer medication or electrical neurostimulation to prevent the onset of the seizure [2, 15, 33].

2.2.4 Seizure Prediction Framework

Seizure prediction studies typically follow a standard structure, as represented in Figure 2.4.

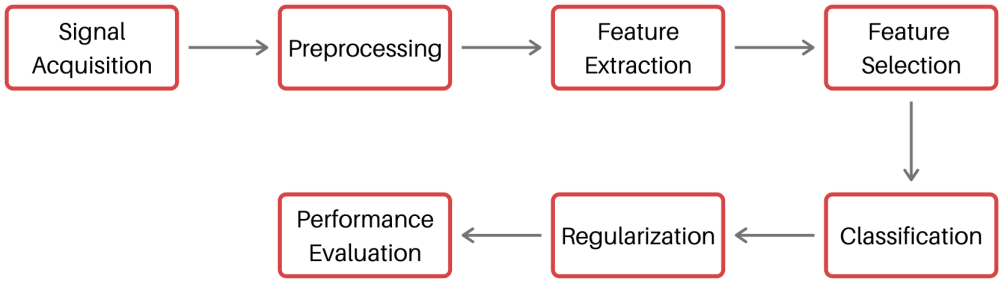
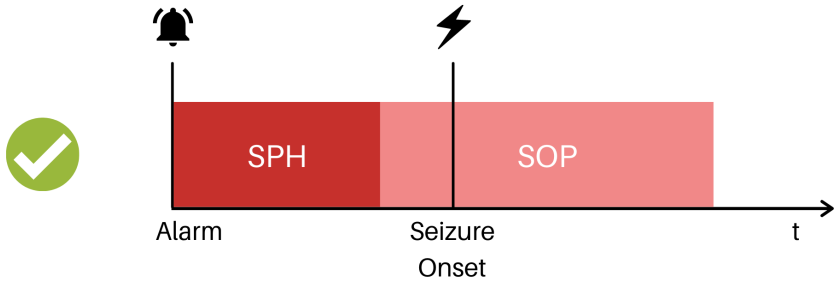


Figure 2.4: Schematic representation of the seizure prediction pipeline. Adapted from: Bou Assi et al. 2017 [2], Kuhlmann et al. 2018 [23]

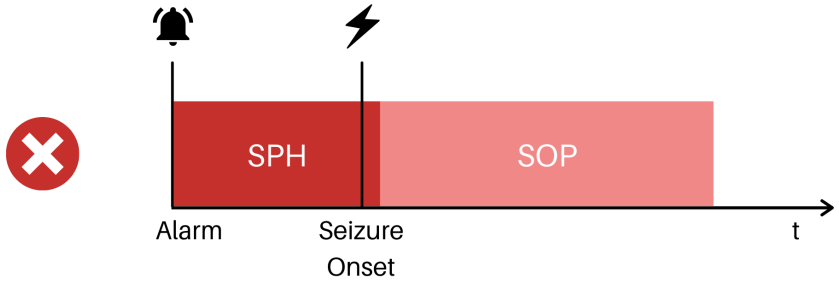
The goal of the preprocessing step, after signal acquisition, is to prepare the signal for feature extraction by enhancing its quality. This includes applying a series of filtering techniques to remove artifacts and increase signal-to-noise ratio [2, 15]. This step is followed by feature extraction and feature selection, where the most discriminant features are extracted. Afterwards, the data is ready for classification, wherein machine learning models are trained to discriminate preictal from non-preictal brain states [2]. Here, regularization is applied to post-process the output, with the goal of lowering the number of false alarms in order to reduce their impact on the patient's life (see Section 2.2.6) [36]. Finally, the results should be evaluated with the standard metrics used in the field of seizure prediction (see Section 2.2.6) and statistically validated (see Section 2.2.7) [2].

2.2.5 Seizure Prediction Characteristic

In 2003, Winterhalder et al. [25] proposed the *Seizure Prediction Characteristic* to evaluate seizure prediction models and allow their fair comparison. The main premise is to assess seizure prediction models based on two metrics, sensitivity and False Positive Rate per Hour (FPR/h) (see Section 2.2.6), and considering the concepts of SOP and SPH. In order for the prediction to be considered as a True Positive (TP), the onset must fall within the SOP (see Figure 2.5). If the seizure begins either during the SPH or after the end of the SOP, it is considered a False Positive (FP) (false alarm). It should be mentioned that, in some studies, the SOP is referred to as SPH and the SPH as Intervention Time (IT) [33, 37, 38].



(a) Correct prediction



(b) False alarm

(c) False alarm

Figure 2.5: Schematic representation of the SPH and SOP and their implication in the determination of True Positives and False Positives: in order for the prediction to be deemed correct, the seizure onset must occur within the SOP. (a) Adapted from Winterhalder et al. 2003 [25]

There are no fixed values for SOP and SPH, as they should be defined according to the requirements of the system being developed and their impact on the patient. In the literature, values of SOP ranging from some minutes to a few hours have been reported [33]. However, the duration of this interval should be carefully addressed, since long SOPs can induce high amounts of stress in the individual, who spends a long time waiting for a seizure which may not even occur. Additionally, for high values of SOP, the performance is no different from a random unspecific predictor [25, 33]. This dependence of the sensitivity on SOP is well illustrated in Figure 2.6, where it is clear how longer SOPs naturally lead to higher sensitivity. It is usual for researchers to consider a SOP with equal duration to the preictal period (see Figure 2.7) [2, 37].

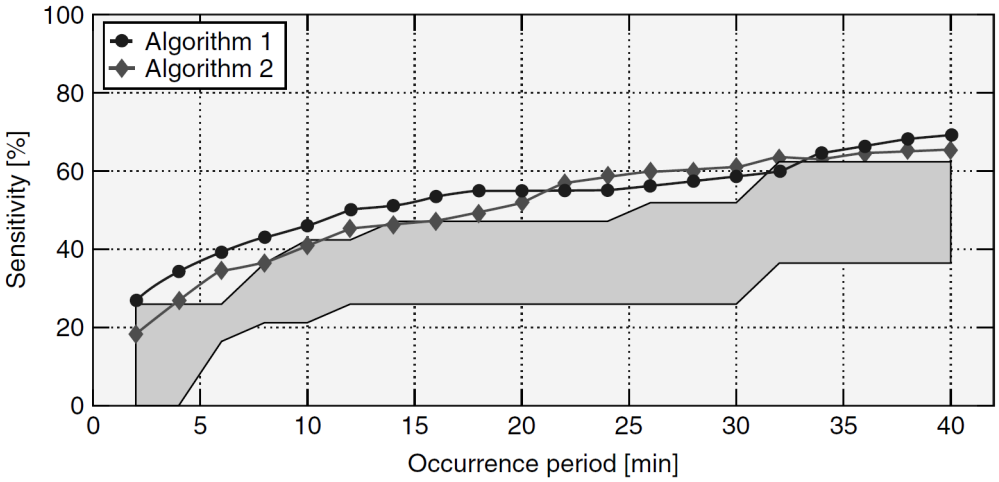


Figure 2.6: Seizure Prediction Characteristic for a fixed SPH of 10 minutes and FPR/h of 0.15, depending on the duration of the SOP. The lines with circles and diamonds represent the values obtained with two seizure prediction algorithms based on long-term intracranial EEG data, and the grey region represents the range of values obtained with a random predictor. Note the increase in sensitivity with the increase of SOP duration. Source: Schelter et al. 2008 [39]

When it comes to SPH, it should provide enough time for preventive action to be taken. Hence, longer intervals are needed for warning systems, whereas shorter intervals can be considered for automated intervention systems, provided that there is enough time for the intervention to take effect [25].

Figure 2.7 depicts the relation between the SOP, SPH and preictal period in the training of the model.

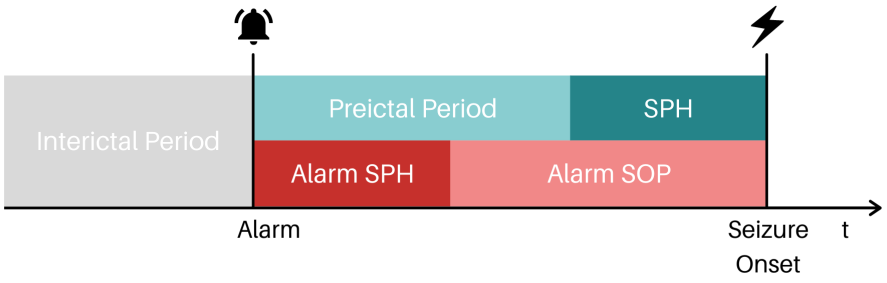


Figure 2.7: Visual representation of the relation between the preictal period, SOP and SPH in the training of the model. The SOP has the exact same duration as the preictal period. The SPH is chosen considering the envisioned application of the model (warning system or closed-loop intervention). During the training phase, the SPH is the period immediately before the seizure onset, preceded by the SOP. A correct alarm should be raised during the preictal period. Afterwards, there is a wait time equal to the SPH, and the seizure is expected within the SOP.

2.2.6 Performance Evaluation

To assess the performance of a given algorithm, it is necessary to calculate some measures of sensitivity and specificity. In standard machine learning problems, such measures are defined based on the confusion matrix (see Table 2.1) [40]. If we regard seizure prediction as a binary problem in which the positive class is the preictal period and the negative class is the interictal, True Positives (TPs) are related to correctly predicted preictal samples, False Positives (FPs) to interictal samples classified as preictal, True Negatives (TNs) to correctly predicted interictal samples, and False Negatives (FNs) to preictal samples classified as interictal.

Table 2.1: Confusion matrix for evaluation of sample performance in Machine Learning problems.

		True Label	
		Preictal	**Interictal**
Predicted Label	**Preictal**	TP	FP
	Interictal	FN	TN

Additionally, sensitivity and specificity would be calculated by applying Equations 2.1 and 2.2, respectively.

$$Sensitivity = \frac{TP}{TP + FN} \tag{2.1}$$

$$Specificity = \frac{TN}{TN + FP} \tag{2.2}$$

However, the aforementioned metrics are not informative in the field of seizure prediction because they are computed based on sample classification, providing no information about the number of correctly predicted seizures or false alarms. Thus, they were adapted to better convey such information, considering the definitions presented in Section 2.2.5 for True Positives and False Positives. Winterhalder et al. [25] proposed the use of the Sensitivity (see Equation 2.3) and the FPR/h.

Nonetheless, there is a lack of consensus when it comes to the definition of FPR/h [33]. In some studies, it is defined considering the full duration of analyzed recordings (see Equation 2.4). In others, the concept of corrected FPR/h is used (see Equation 2.5), considering only the time length during which alarms can actually be fired. This is important because when an alarm is fired, there may be a time period during which the algorithm is idle, i.e., no alarms can be fired. This period is called

refractory period and is usually equal to the sum of the duration of SOP and SPH. Such divergences should be considered when making comparisons between studies reporting their performance in terms of FPR/h [33]. Some authors also proposed the use of the portion of time under false warning instead of the FPR/h [33, 37, 41].

$$Sensitivity = \frac{TP}{All\ seizures} \tag{2.3}$$

$$FPR/h = \frac{FP}{Total\ time\ analyzed} \tag{2.4}$$

$$FPR/h_{corrected} = \frac{FP}{Interictal\ duration - FP \times (SOP + SPH)} \tag{2.5}$$

Herein, performance metrics will be reported by means of sensitivity (Equation 2.3) and corrected FPR/h (Equation 2.5). Figure 2.8 presents an example of the assessment of the performance of system prediction models using these metrics.

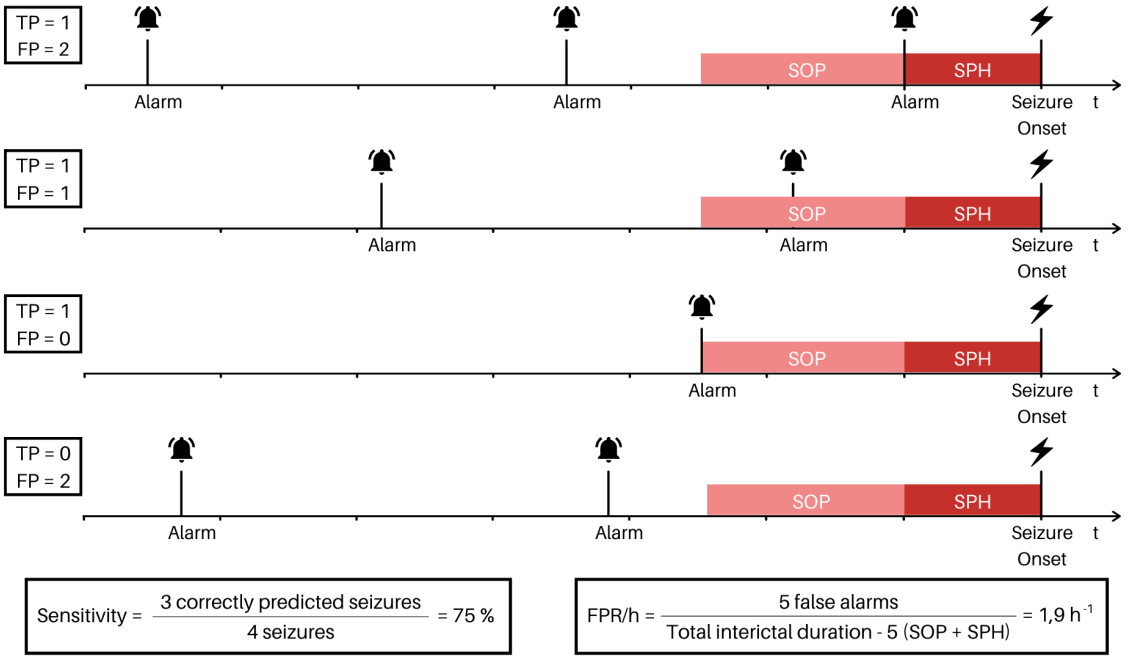


Figure 2.8: Example of the computation of the performance metrics. Here, a SOP of 15 minutes and an SPH of 10 minutes are considered. Each division in the time axis (x-axis) corresponds to 10 minutes.

The sensitivity should always be reported alongside the FPR/h, since there is a trade-off between both metrics. This means that the model can be tuned in order to obtain very high sensitivity values at the expense of high FPR/h values, and

vice-versa. This relationship can be observed in Figure 2.9, where it is clear how the increase in one of the metrics implies an increase in the other.

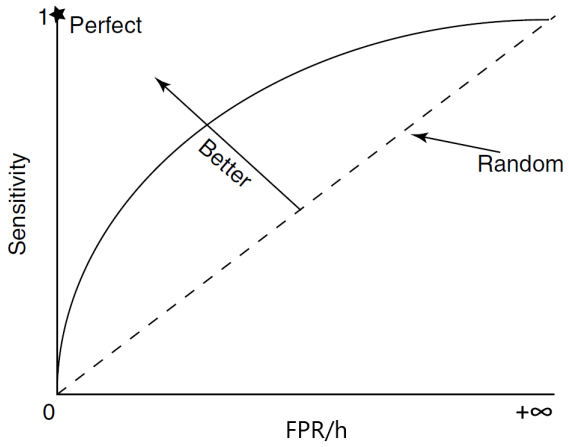


Figure 2.9: Example of a ROC curve (solid line). The dashed line represents the performance of a random predictor. The star denotes the optimal performance values. Adapted from: Schelter et al. 2008 [39]

Since achieving the optimal performance values of 100% sensitivity and 0 FPR/h is a utopian goal, it is essential to define the required trade-off between both measures. This means evaluating the cost of False Positives and False Negatives to the patient, which varies according to the type of system being developed.

When developing an alarm system, high FPR/h values should be avoided since they can induce anxiety in the patient, eventually causing them to lose confidence in the system. On the other hand, if closed-loop systems are considered, higher FPR/h values can be tolerated, thus leading to higher sensitivity values, if the intervention technique (e.g., electrical stimulation, on-demand medication) is non-invasive or does not produce serious side effects [25, 33, 39]. Additionally, a maximum threshold can be defined based on the average incidence of seizures. In pre-surgical monitoring, the average incidence is 3.6 seizures a day (0.15 seizures per hour), an uncommonly high value due to the reduction of AED intake. On the other hand, DRE patients under normal conditions suffer about 3 seizures per month (0.0042 seizures per hour) [25]. Taking this into account, Winterhalder et al. [25] proposed maximum values of $\mathrm{FPR/h_{max}} = 0.15\ \mathrm{h^{-1}}$ for patients under pre-surgical monitoring and $\mathrm{FPR/h_{max}} = 0.0042\ \mathrm{h^{-1}}$ for DRE patients under normal conditions.

Regarding sensitivity, Schulze-Bonhage [42] reported that the majority of the patients required a seizure prediction system to correctly predict at least 90% of seizures in order to be considered useful.

In sum, the seizure prediction characteristic evaluates the model's performance by measuring the dependence of the sensitivity on the maximum False Prediction Rate (FPR_{max}), the SOP and the SPH [25].

2.2.7 Statistical Validation

Besides yielding satisfactory performance values, a seizure prediction model must also be proven to perform above chance level, since non-null sensitivity and relatively low values of FPR/h can be obtained without a valid model [43]. Several methods have been proposed to perform this statistical validation, such as comparisons with (i) analytical random predictors, (ii) periodical predictors, (iii) baseline predictors, (iv) area under the receiver operating curve (AUC), and (v) surrogate methods. Another alternative for comparisons between different studies is non-parametric testing [2, 25, 39].

Throughout this section, the most used statistical validation methods will be further explained.

2.2.7.1 Analytical Predictors

The analytical predictors encompass random and periodic predictors.

Random Predictor

Winterhalder et al. [25] proposed a random predictor in which alarms are raised randomly without use of any information (e.g. EEG or ECG). Herein, the parameters of the prediction method are adjusted so that $FPR/h = FPR/h_{max}$. Thus, the probability of raising one alarm during a small interictal time interval, I, is given by

$$P = FPR/h_{max} \cdot I. \tag{2.6}$$

Considering a longer interval, W, the probability of at least one alarm occurring is given by

$$P = 1 - (1 - FPR/h_{max} \cdot I)^{W/I} \approx 1 - e^{-FPR/h_{max} \cdot W}, \ for\ I \ll W. \tag{2.7}$$

Thus, for $W = SOP$, this is the sensitivity of the random predictor.

Schelter et al. [39, 44] also proposed a random predictor, which generates alarms randomly following a homogeneous Poisson process for the false predictions. Herein,

the probability of raising an alarm at any sampling point of a time series is

$$P_{Poiss} = \frac{FP}{N}, \tag{2.8}$$

where FP is the number of false-positive predictions and N is the number of samples.

Let us consider a time period of duration equal to SOP, and that the product $FPR/h_{max} \cdot SOP$ is considerably lower than one, which is a reasonable assumption if we suppose that the patient is not under continuous warning. Then, the probability of at least one alarm being raised within the SOP period for a certain value of FPR/h_{max} can be approximated by

$$P \approx 1 - e^{-FPR/h_{max} \cdot SOP} \approx FPR/h_{max} \cdot SOP. \tag{2.9}$$

The probability P forms the basis of a significance level that allows to test if the sensitivity *S(FPR/h_{max}, SOP, SPH)* of a given prediction method is higher than that of a random predictor.

The proposed method also enables the analysis of more than one seizure and the consideration of the number of predictors used. Thus, the probability of predicting at least k out of K seizures using d predictors is

$$P_{binom,d}(k, K, P) = \left[\sum_{j \leqslant k} \left(P^j (1-P)^{K-j} \right) \right]^d. \tag{2.10}$$

Taking this into account, the critical value, σ_{low}, to test the statistical significance of the random predictor is given by

$$\sigma_{low} = \frac{argmax_k \{ P_{binom,d}(k, K, P) > \alpha \}}{K} \cdot 100\%, \tag{2.11}$$

where α is the significance level.

Periodical Predictor

Winterhalder et al. [25] proposed a periodical predictor which raises alarms periodically. Here, the probability of raising an alarm during SOP is given by

$$P = min\{FPR/h_{max} \cdot SOPs, 100\%\}, \tag{2.12}$$

which is the sensitivity of the periodical predictor.

2.2.7.2 Surrogate Time-Series Analysis

Surrogate time-series analysis is a Monte Carlo based method which consists in applying constrained randomizations to the data. If the performance of the seizure prediction model is higher for the original data than for the surrogate data, then the model can be said to perform better than chance [39]. Based on this concept, two methods have been proposed: seizure-time surrogates and measure-profile surrogates.

Seizure-Time Surrogates

Andrzejak et al. [45] proposed the seizure-times surrogates, which consists in shuffling the original seizure onset times, while maintaining the order of the input data (see Figure 2.10).

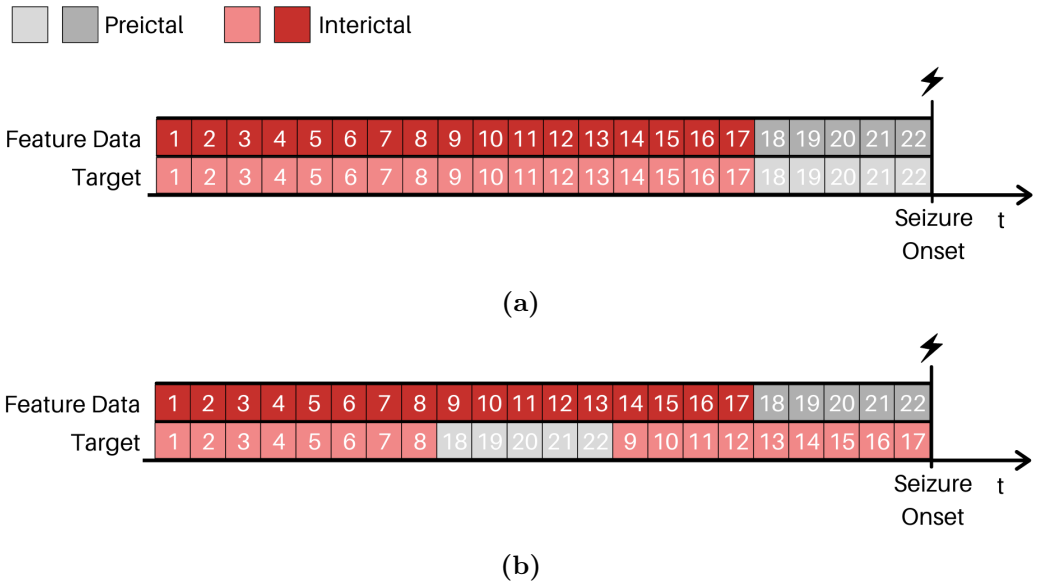


Figure 2.10: Seizure time-surrogate analysis examples. (a) Original feature data and labels. (b) Example of surrogate time-series where the seizure onset time is randomly shuffled.

Measure-Profile Surrogates

Kreuz et al. [46] proposed the measure-profile surrogates, in which the feature data (measure-profiles) is randomized, while the original onset times are maintained (see Figure 2.11).

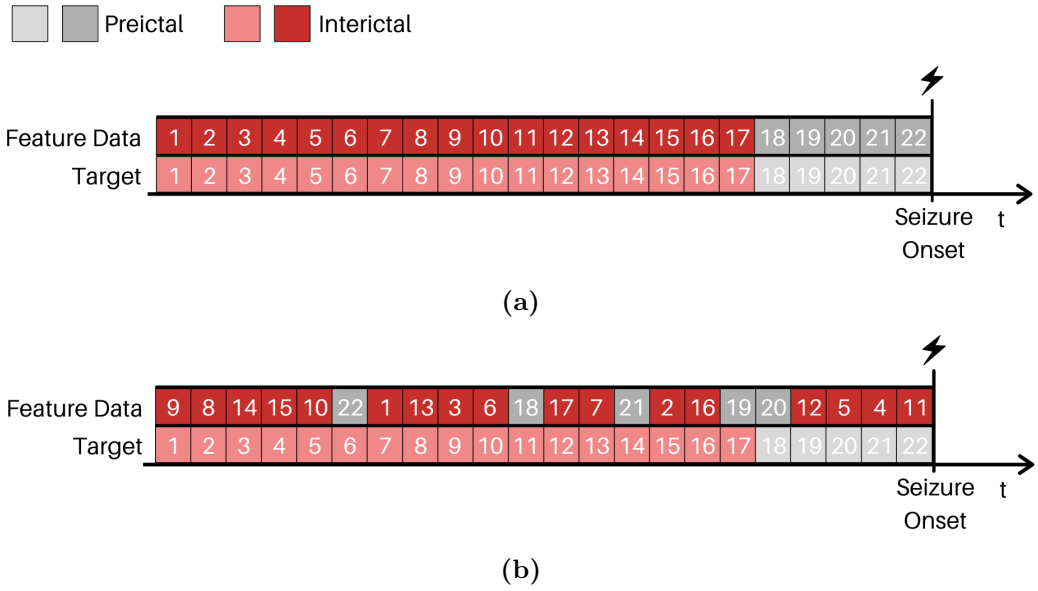


Figure 2.11: Measure-profile surrogate analysis examples. (a) Original feature data and labels. (b) Example of surrogate measure-profiles where the feature data is randomly shuffled.

2.2.7.3 Overview

All of the methods discussed above present some advantages and disadvantages, and the choice of the statistical validation method should be made considering the model's characteristics.

When it comes to analytical predictors, they are simple and easy to apply, since all that is needed is to compute the sensitivity of the random predictor using the expressions presented above (see Section 2.2.7.1) and to compare them to the value obtained with the model under analysis. However, such methods might sometimes be too conservative from the statistical point of view, as well as slightly less powerful [47].

Regarding surrogate time-series analysis, on the one hand, these methods are computationally more complex than analytical predictors. On the other hand, they are more flexible, allowing the inclusion of several constraints and assumptions to test different null-hypothesis [43], and offer a more solid validation, providing greater confidence in the results [48]. However, they can lead to inaccurate conclusions if the null-hypothesis is inadequate [2, 47]. Additionally, the measure-profiles surrogate analysis is more complex than the time-series surrogate, since there is the need to retest the model in order to perform the statistical analysis.

Taking into account all of the discussed above, herein, statistical validation of the developed methodologies will be carried out using the seizure-times surrogate

analysis, since it provides the best trade-off between power and complexity.

2.2.8 Data Imbalance

An important problem to consider when developing machine learning models, particularly seizure prediction models, is class imbalance. This happens when one of the classes, typically the most relevant one (positive class) is seriously underrepresented. In the particular case of seizure prediction, the preictal period is typically much shorter than the interictal, which creates an unwanted bias towards the interictal period. To counter the effects of class imbalance, undersampling of the interictal class coupled with ensemble techniques have been widely used in seizure prediction [49].

2.3 Electrocardiogram (ECG)

The Electrocardiogram (ECG) is a clinical exam which produces a representation of the cardiac activity over time in a time-voltage graph, recording voltages using electrodes placed at the surface of the skin [50].

In its normal state, the tissues of the heart are polarized. The electrical activation of the heart tissues is called depolarization, while its return to the normal (resting) state is called repolarization. In one cardiac cycle, the atria are depolarized, pumping blood to the ventricles, followed by the depolarization of the ventricles, to pump blood to circulation. Finally, the ventricles repolarize. These potential differences are reflected in the ECG profile [51].

The normal ECG morphology includes five basic waveforms (see Figure 2.12). P waves correspond to atrial depolarization, the QRS complex represents ventricular depolarization, and the ST segments, T wave and U wave (this last one not always visible) are related to ventricular repolarization [51].

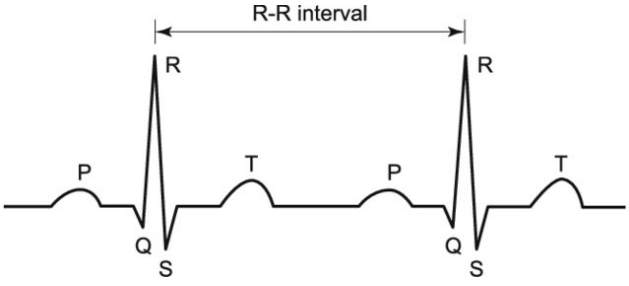


Figure 2.12: Representation of the normal ECG morphology, including the basic waveforms. Source: Bou Assi et al. 2017 [2]

Different ECG leads record different perspectives of the electrical potential of the heart. Thus, depending on the electrode configuration, different outlines are obtained (see Figure 2.13) [52]. From the data available in an ECG signal, it is possible to determine the interval between two consecutive R waves (R-R Interval), which is the basis of Heart Rate Variability (HRV) studies [51].

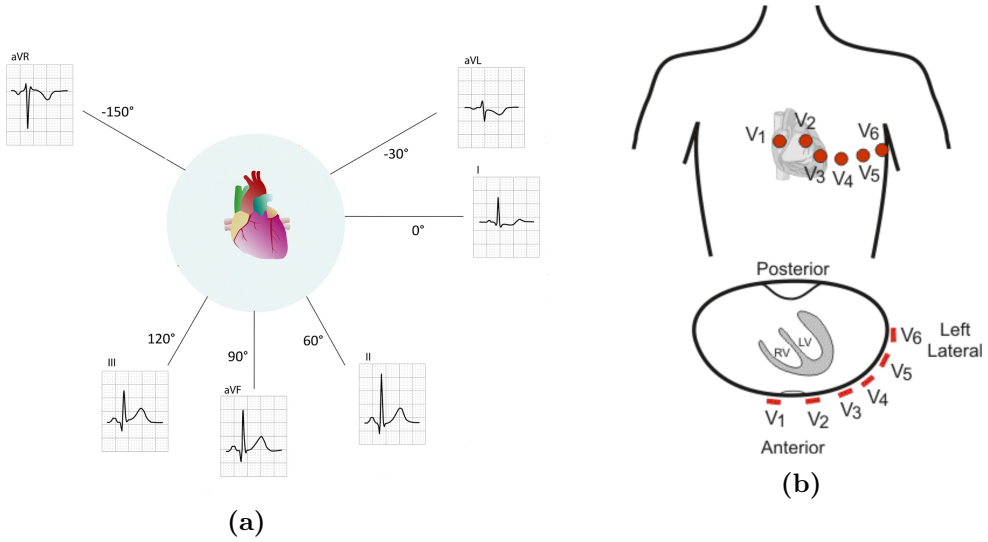


Figure 2.13: ECG electrode configurations. (a) Six limb leads: three unipolar leads (I, II and III) and three augmented unipolar leads (aVR, aVL and aVF) and respective ECG patterns. Adapted from: Lindow et al. 2019 [53]. (b) Six unipolar chest leads (V_1 to V_6). Source: `https://www.cvphysiology.com/Arrhythmias/A013c`

Based on the ECG signal, it is possible to compute the Heart Rate (HR) and Heart Rate Variability (HRV), which can provide information about cardiac and autonomic functions.

2.3.1 Heart Rate (HR)

The HR is a measure of the number of heartbeats per minute. To obtain its values it is necessary to detect the QRS complexes and calculate the R-R Intervals (RRIs). The instantaneous HR is given by the ratio *60/RRI*, where RRI is measured in seconds [51].

2.3.2 Heart Rate Variability (HRV)

HRV is a measure of the variability of R-R Intervals. The RRI represents the time interval between two consecutive R waves. Thus, HRV is measured by detecting

the QRS complexes and computing the intervals between consecutive complexes [13]. After computing the RRIs, they can be plotted in a tachogram (see Figure 2.14).

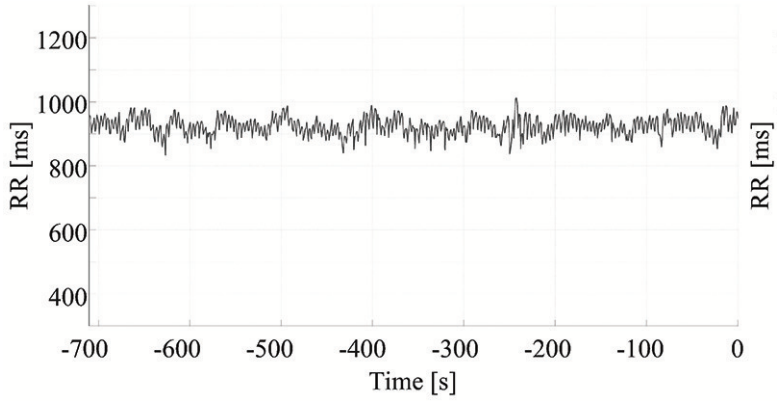


Figure 2.14: HRV tachogram. Source: Pavei et al. 2017 [54]

2.4 Autonomic Nervous System (ANS)

The Autonomic Nervous System (ANS) works to maintain homeostasis by regulating several key visceral functions, including the cardiovascular and gastrointestinal systems, body temperature and sweating [13, 17]. The ANS is subdivided into the sympathetic and parasympathetic systems.

The ANS's responses are influenced by the anterior cingulate, insular, posterior, orbito-frontal and pre-frontal cortices, as well as the amygdala and hypothalamus. Thus, if abnormal brain activity propagates to these areas in the brain, it is plausible that the ANS will be affected, activating/inhibiting the sympathetic and/or parasympathetic regions [13, 17, 21].

The sympathetic nervous system is connected to the heart by neurons from the rostral ventrolateral medulla. Its stimulation results in increase in Heart Rate (HR), Blood Pressure (BP), conduction and excitability of the heart. On the other hand, the parasympathetic nervous system is connected to the heart by the vagus nerve. When this pathway is activated, the result is the opposite: decrease in Heart Rate (HR), Blood Pressure (BP), conduction and excitability [17, 21].

Following this line of thought, cardiac parameters, such as Heart Rate (HR), Blood Pressure (BP) and Heart Rate Variability (HRV), have been pointed as potential biomarkers in the evaluation of ANS function [13]. However, Heart Rate and Blood Pressure are unable to provide information about the branch of the ANS that has been activated. In fact, the only information they provide is that there has been a change in autonomic control [13]. HRV, on the other hand, can provide

direct information about the sympatho-vagal balance [13, 55]. Increased HRV indicates a predominance of parasympathetic activity, while decreased HRV suggests a dominance of sympathetic control (see Figure 2.15) [55].

Figure 2.15: HRV as a measure of ANS balance. Increased HRV indicates predominance of parasympathetic activity, while decreased HRV indicates predominance of sympathetic activity. Source: Myers et al. 2018 [55]

However, some aspects should be taken into account when considering inspection of the autonomic function to predict epilepsy, such as the effects of the circadian cycles, changes in AED intake, and inter-patient variability [13].

2.5 Cardiovascular Changes Related to Epileptic Seizures

As previously stated in Section 2.4, the propagation of abnormal brain dynamics, such as seizure discharges, to brain structures involved in ANS control can affect autonomic function [13, 17, 21]. In fact, many studies suggest that the occurrence of seizures causes changes in autonomic function not only during the seizure itself, but also during the remaining periods. This can affect the activity of the parasympathetic and sympathetic systems, resulting in autonomic symptoms such as alterations in cardio-respiratory function [56]. More specifically, the activation of the sympathetic nervous system during seizures provokes increase in Blood Pressure (BP), Heart Rate (HR) and, possibly, tachycardia and tachypnea. On the other hand, activation of the parasympathetic nervous system causes decrease in Blood Pressure (BP) and Heart Rate (HR) [17, 56].

It has been postulated that seizures with a right-sided focus result in tachycardia, while seizures with left-sided focus result in bradycardia [57]. This lateralization hypothesis suggests that stimulation of the right insular cortex may trigger activation of the sympathetic nervous system, while stimulation of the left cortex might activate the parasympathetic nervous system [58, 59]. Several research studies have obtained results that support this theory [57, 60]. Additionally, the lateralization

patterns appear to vary between patients [13].

The most common changes related to epileptic seizures are tachycardia or increase in Heart Rate and Blood Pressure. Less frequently, bradycardia or decrease in Heart Rate and Blood Pressure are observed. Other autonomic manifestations include palpitations, arrhythmias and asystole, the latter being very rare. Such abnormalities in cardiovascular function are suggested to be more prominent in generalized than in non-generalized seizures [17, 56]. These cardiac changes can also increase the risk of SUDEP, especially when combined with other factors such as alterations in the respiratory system [56] Postictal arrhythmias, although rare, represent increased likelihood of SUDEP when compared to ictal arrhythmias [61].

In addition, recurrent and excessive stimulation of the ANS due to seizure events has also been shown to result in long-lasting defects in cardiac tissue and function, increasing the probability of arrhythmias and ischemia [17, 62]. It can also be linked to chronic dysfunction in autonomic control, found in 56.3% of patients with DRE. This effect is more commonly observed in children than in adult patients [17].

2.5.1 Changes in Heart Rate (HR)

A percentage in the range of 38% - 100% of patients with epilepsy have suffered from significant HR changes in at least one of their seizures [21]. The changes start a few seconds before or at the electrographic onset and may last for minutes to hours after the seizure [58]. Inclusively, if more seizures occur before the HR stabilizes, the changes can be incremental.

Unfortunately, high variability is evident across studies regarding changes in HR resulting from epileptic seizures. This can be attributed to many factors, such as the age of the subjects, type of seizures, AED intake, seizure onset lobe, and cardiac co-morbidities [13, 21, 63]. In fact, Osorio et al. [64] reported that the probability of detection of a seizure based on HR changes varied with age, gender, seizure type, etiology, and time since the diagnosis of epilepsy.

This prompted researchers to conduct studies to assess the differences in HR between the preictal, ictal and postictal states. In a study conducted on 58 DRE patients, Leutmezer et al. [60] reported preictal HR changes in 75.9% of seizures. In another study with 30 DRE patients, Zare et al. [65] reported significant differences in HR between the preictal, ictal and postictal periods. In general, such changes seem to be more common in temporal lobe seizures when compared to extratemporal seizures [21, 60, 65].

Importantly, the patterns of HR changes have been reported to be similar across

different seizures from the same patient, suggesting that ANS operates in a standardized manner within each patient [58].

2.5.1.1 Tachycardia/Heart Rate Increase

Tachycardia is the most common HR abnormality related to seizures and refers to the increase in HR past a certain threshold, defined relatively to the resting HR. As this value depends on several factors, namely age, the upper normal HR is 100 bpm (beats per minute) for adults (more than 15 years old) and 169 bpm for infants (6-11 months old) [21].

Tachycardia can happen before (0.7 s to 49.3 s), during or after the ictal period. This effect seems to happen more often in right temporal seizures, which supports the hypothesis of this alteration being caused by epileptic discharges on the right insular cortex and the lateralization of ANS control [17, 21].

Preictal HR increase has been reported in 21.1%-28% of seizures [21, 63], and has been found to be more common in mesial temporal lobe seizures than non-lesional temporal lobe or extra-temporal lobe seizures [60, 63]. Some studies claim that this effect is more notorious in right-sided mesial seizures. FBTC seizures have also been linked to higher preictal HR [63]. Generally, HR increase occurs earlier in Temporal Lobe Epilepsy (TLE) patients ($\sim$13 seconds before seizure onset), when compared to patients with Extratemporal Lobe Epilepsy (XTLE) ($\sim$8 seconds before seizure onset) [17, 56]. HR increase was found more often in adults when compared to pediatric patients. It also seems more recurrent in male patients and patients undergoing AED treatment [63].

Ictal tachycardia is estimated to affect about 82% of patients with epilepsy [21]. Additionally, it has been reported in 52% - 100% of seizures, more specifically in 32.9% - 100% of focal seizures and in 48% - 100% of generalized seizures [21, 63].

In rare cases, tachycardia might evolve to ventricular fibrillation, resulting in SUDEP [61].

2.5.1.2 Bradycardia/Heart Rate Decrease

Bradycardia is less commonly observed. It is characterized by a decrease in HR below a certain threshold, and is thought to be caused by epileptic discharges on the left insular cortex or amygdalae. This assumption is supported by the fact that this alteration is predominant in left-sided seizures [17, 21]. In addition, it is more common in temporal and frontal seizures [58]. This type of parasympathetic response also seems more frequent in male patients [56].

Ictal bradycardia occurs in less than 5% of patients and in 2% - 3.7% of seizures [56, 60, 63]. Although rare, the occurrence of ictal bradycardia is potentially dangerous as it can trigger syncope and lead to accidents. Most importantly, it can also cause asystole, which in turn may lead to SUDEP [17]. Asystole has been reported to be more common in TLE [61].

Ictal asystole has been reported to affect 0.318% of DRE patients, occurring only in focal epilepsy [61]. In other studies, the percentages of patients affected by ictal asystole were 0.4% and 0.27% [58]. Long-term monitoring revealed higher percentages, in the range 5%-16% [66, 67]. The following hypotheses have been put forward to explain the causes of ictal asystole:

- Direct stimulation of the ANS [62];
- Fear induced by the seizure, which in turn can cause cardioinhibition and vasodilation [61].

Postictal asystole is an even rarer event, associated with convulsive seizures [61, 62]. However, it has been linked to higher fatality rates [62].

2.5.2 Changes in Electrocardiogram (ECG) Morphology

Abnormalities in ECG morphology occurring during the ictal period may be observed in 35% of generalized seizures. Besides, it is estimated that 40% of patients suffering from DRE show abnormalities in rhythm or repolarization during seizures or in the moments after, which can be reflected in the ECG [17, 56].

These alterations might be more or less severe, with the most severe including ST-depression and T-wave inversion, which occur in 6-13% of seizures [56]. In other studies, ictal ST-depression was found in 40% of patients, while T-wave inversion was reported in 10% of the individuals. Such ECG morphological changes are indicative of cardiac ischaemia and occurred more often during ictal tachycardia [57].

Additionally, in a study conducted by Surges et al. [68] on 25 DRE patients with TLE, QTc[1]-shortening was found in 68% of patients, mainly in the postictal phase and in FBTC seizures. Lengthening of the QTc was also observed in 6% of seizures and 12% of patients.

[1]QTc: Corrected value of the QT interval to account for inter-patient variability in HR.

3

State of the Art

This Chapter presents a discussion of the state of the art in preictal analysis based on Heart Rate Variability (HRV), in Section 3.1. Afterwards, in Section 3.2, a brief overview of the state of the art in identification of the preictal period is presented. Finally, Section 3.3 discusses the state of the art in seizure detection and prediction, focusing on studies based on HRV. This Section culminates in a brief analysis of the current shortcomings of seizure prediction and detection studies.

3.1 Preictal Analysis Based on Heart Rate Variability (HRV) Features

As discussed in Section 2.4, HRV can be used to provide direct information about Autonomic Nervous System (ANS) activity at any given moment. Thus, it has been widely used to assess autonomic function in patients with epilepsy and in seizure detection and prediction studies.

In fact, patients with epilepsy have been reported to have lower HRV values when compared to healthy subjects [58, 59]. Furthermore, Drug Resistant Epilepsy (DRE) patients show even lower values of HRV than non-DRE patients [17, 58]. This fact reflects an impairment in autonomic function and sympathovagal imbalance, which can in turn trigger arrhythmias and culminate in Sudden Unexpected Death in Epilepsy (SUDEP) [5, 17, 58, 59]. Such imbalance is translated into an increase of sympathetic tone and/or decrease of parasympathetic tone [13, 17], both of which are usually found in DRE [5].

Regarding Temporal Lobe Epilepsy (TLE), changes in HRV have been found mostly in patients with a higher frequency of seizures. In patients with DRE, a progressive reduction of HRV has been found with the increase of time with epilepsy, while no further decrease was detected in non-DRE patients [5].

Interestingly, there appear to be differences in the extent of HRV alteration between men and women. Behabahani et al. [69] reported a greater percentage of

changes in male subjects when compared to females. Additionally, men presented a predominance of parasympathetic over sympathetic activity, while the opposite was true for women. This may explain the higher likelihood of arrhythmias and consequent SUDEP in men.

Furthermore, Anti-Epileptic Drugs (AEDs) can also alter the sympathovagal balance and, consequently, HRV [17, 59]. The same can be said of circadian patterns [57]. Thus, gender, AED intake and circadian rhythms should be taken into account in any HRV analysis.

Different metrics can be extracted from the HRV to perform a thorough analysis of ANS influence on the cardiac function, which will be presented in Section 3.1.1.

3.1.1 Heart Rate Variability (HRV) Features

HRV can be analyzed through linear and non-linear methods, the former comprising the time and frequency domain analysis.

Time-domain Analysis

Time-domain features are related to cardiovascular system activity. Table 3.1 presents an overview of the time-domain features most used in seizure prediction and detection and their relation to the sympathovagal balance.

Table 3.1: Features extracted from the time-domain analysis. The characterization column presents information on the relation between each feature and the ANS function.

Features	Definition	Characterization
RRMean [14, 70, 71]	Mean of the RRI time-series	*
RRMin [22]	Minimum of the RRI time-series	*
RRMax [22]	Maximum of the RRI time-series	*
RRVar [22]	Variance of the RRI time-series	*
SDNN [14, 22, 70]	Standard deviation of RRIs	OV
NN50 [22, 70]	Number of RRIs which last more than 50 ms	STV, PSA
pNN50 [14, 22, 70]	Percentage of RRIs which last more than 50 ms	STV, PSA
RMSSD [14, 22, 70]	Root mean square of successive differences	STV, PSA
SDSD [22]	Standard deviation of successive differences	STV, PSA
Triangular Index [14, 71]	Integral of the histogram of RRIs divided by the maximum height of the histogram	*

STV: short-term variability; PSA: Parasympathetic activity; OV: Overall variability; *No information available.

Frequency-domain Analysis

Frequency-domain analysis is related to the balance between the sympathetic and parasympathetic branches of the ANS and is based on the computation of the power spectral density. The spectrum can be divided into three frequency bands: Very Low Frequency (VLF) band, Low Frequency (LF) band and High Frequency (HF) band (see Figure 3.1) [14, 17].

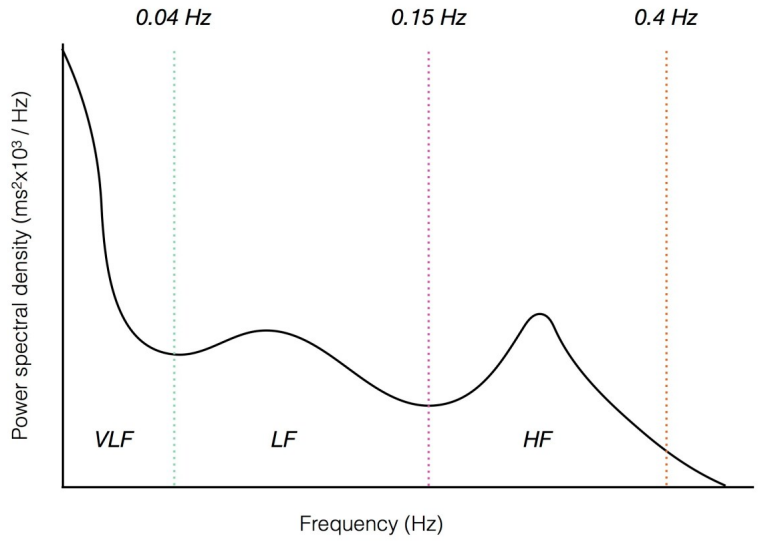


Figure 3.1: Estimation of power spectral density of HRV in order to compute power in the three frequency bands of interest. Source: `http://timingforum.org/time-perception-and-the-heart/#fnr8-16561`

Table 3.2 presents an overview of frequency-domain features, including the definition of the three frequency bands mentioned above.

Table 3.2: Features extracted from the frequency-domain analysis. The characterization column presents information on the relation between each feature and the ANS function.

Features	Definition	Characterization
VLF Power [14, 17, 22]	Power of the VLF band (0.003 - 0.040 Hz)	LTV
LF Power [14, 17]	Power of the LF band (0.040 - 0.15 Hz)	SA
HF Power [14, 17, 22]	Power of the HF band (0.15 - 0.40 Hz)	STV, PSA
Total Power (TP) [22]	Total power of the window	OV
LF/HF [14]	Ratio of LF power to HF power	SVB

STV: short-term variability; LTV: Long-term variability; PSA: Parasympathetic activity; SA: Sympathetic activity; SVB: Sympatho-vagal balance; OV: Overall variability.

Non-Linear Analysis

Since physiological systems are inherently non-linear, some of their properties will be missed when applying linear methods. Non-linear HRV features include measures of entropy, Detrended Flunctuation Analysis (DFA), Poincaré plots, and Recurrence Quantification Analysis (RQA) (see Table 3.3).

Detrended Flunctuation Analysis (DFA) consists in the computation of the log-log graph of *F(n)* against n, where *F(n)* is the root mean square flunctuation of the integrated and detrended data in windows of length n (see Figure 3.2). Afterwards, linear regression is applied to the data in order to extract two measures: α_1 and α_2 (see table 3.3) [72].

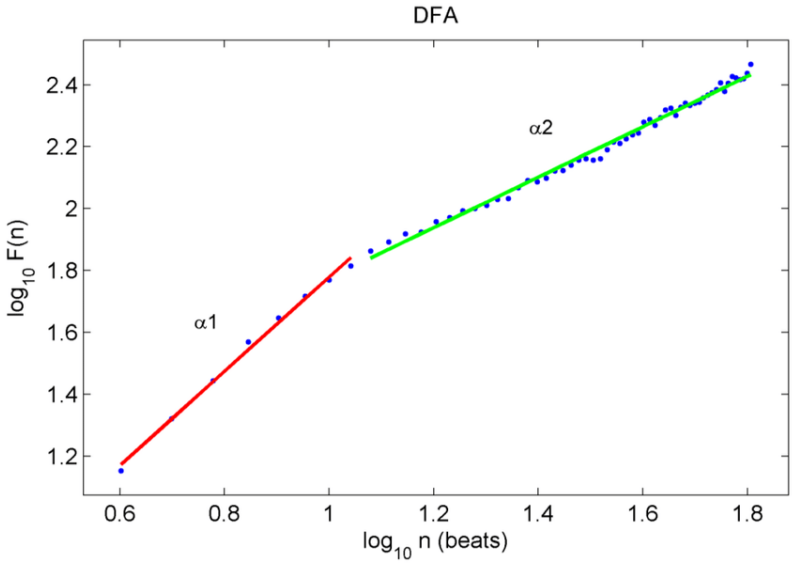


Figure 3.2: Detrended flunctuation analysis using healthy human data. The measures α_1 and α_2 correspond to the slopes of the linear regression lines. Source: Ramshur 2010 [73]

The Poincaré plot is obtained by computing a scatter plot of *RRI(n)* against *RRI(n-1)*. This data is fitted by an ellipse, allowing the extraction of two measures, SD_1 and SD_2, the length of the minor and major axis of the ellipse, respectively (see Figure 3.3) [14, 22]. Additionally, three other features can be derived from these: SD_1/SD_2, Cardiac Sympathetic Index (CSI) and Cardiac Vagal Index (CVI) (see Table 3.3).

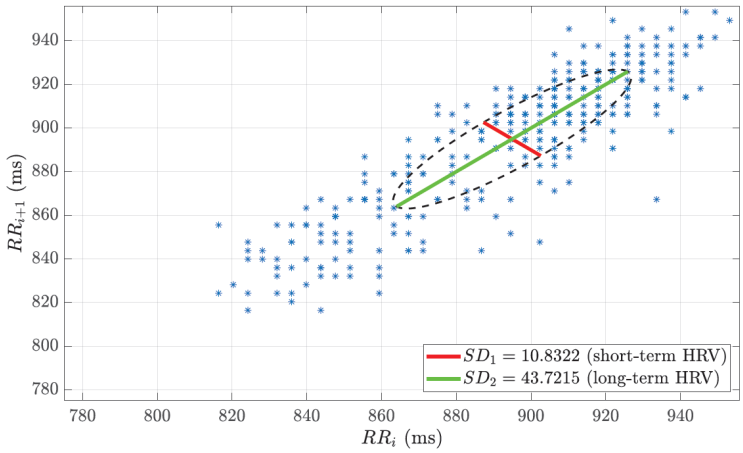


Figure 3.3: Example of a Poincaré plot computed from a 5-min window ranging from 78 to 73 minutes before seizure onset. SD_1 is the length of the minor axis of the ellipse and SD_2 is the length of the major axis. Source: Leal et al. 2021 [22]

Recurrence Quantification Analysis (RQA) involves computing the recurrence plot, which represents the pairwise Euclidean distance between samples (see Figure 3.4). RQA allows to obtain several measures of complexity which quantify the recurrence point density and the existence of diagonal/vertical lines in the recurrence plot (see Table 3.3) [22, 70].

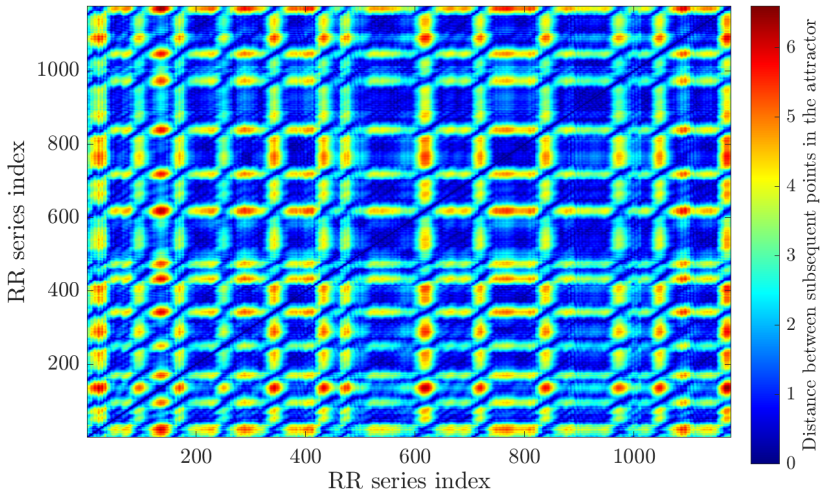


Figure 3.4: Example of a colour recurrence plot computed from a 5-min window ranging from 78 to 73 minutes before seizure onset. Source: Leal et al. 2021 [22]

Table 3.3 presents an overview of the non-linear features most often used in the field of seizure prediction and detection.

Table 3.3: Features extracted from the non-linear analysis. The characterization column presents information on the relation between each feature and ANS function.

Features	Definition	Characterization
ApEn [14, 22]	Approximate Entropy	STV, PSA
SampEn [22, 54]	Sample entropy	SVB
	Detrended Flunctuation Analysis (DFA)	
α_1 [22]	Slope of the linear regression of the data in the range 4-11 heartbeats	STV
α_2 [22]	Slope of the linear regression of the data in the range 11-64 heartbeats	LTV, SA
	Poincaré Plot	
SD_1 [14, 22, 70]	Minor axis of the ellipse	STV, PSA
SD_2 [70, 74–76]	Major axis of the ellipse	LTV, OV
SD_1/SD_2 [14, 22, 74]	Ratio of SD_1 to SD_2	SVB
CSI [70]	Cardiac Sympathetic Index	*
CVI [70]	Cardiac Vagal Index	*
	Recurrence Quantification Analysis (RQA)	
Rec [70]	Recurrence rate	*
Det [70]	Determinism	*
L [70]	Average length of the diagonal line	*
L_{max} [70]	Length of the longest diagonal line	*
TT [70]	Laminarity	*
Ent [70]	Shannon entropy	*

STV: short-term variability; LTV: Long-term variability; PSA: Parasympathetic activity; SA: Sympathetic activity; SVB: Sympatho-vagal balance; OV: Overall variability; *No information found.

Despite being widely used in cardiac function evaluation, non-linear methods do not directly measure autonomic function. However, like previously stated, non-linear properties of the system are not taken into account when using linear methods. In addition, non-linear properties provide better repeatability across measurements. Moreover, the non-stationarity of the ECG signal may render non-linear methods more informative compared to time and frequency-domain HRV parameters [13, 71].

3.1.2 Differences in Heart Rate Variability (HRV) Between Preictal and Interictal Periods

Some statistical analysis studies have been conducted to determine if there are significant differences in HRV features between preictal and interictal periods, in order to evaluate whether seizure prediction based on HRV parameters is feasible. Table 3.4 presents some of these studies in order to analyze the characteristics of the dataset used as well as their main conclusions.

Table 3.4: HRV-based statistical analysis studies to evaluate differences between preictal and interictal periods in patients with epilepsy.

Authors	Dataset	Methodology		Results/Conclusions
		Feature Extraction	Statistical Analysis	
Behbahani et al. 2013 [71]	EPILEPSIAE database. 12 DRE patients (7 male + 5 female, age = 43,01 ± 10,16 years). Various types of epilepsy. Total of 133 seizures.	**Time-domain:** Triangular Index; **Frequency-domain:** LF, HF, LF/HF; **Non-linear:** Poincaré plot (SD_1, SD_2, CSI).	Paired t-test Comparison of intervals of 240, 90-30, 30-10, 10-5 and 5-0 minutes prior to seizure onset.	Increase in LF/HF and CSI 30 minutes before seizure onset, more significant in the last 5 minutes. Gradual decrease of triangular index before seizure onset.
Moridani et al. 2017 [77]	PhysioNet database. 2 hour long recordings. 7 patients with focal epilepsy.[2] Total 11 seizures.	**Time-domain:** MeanNN, SDNN, RMSSD, NN50, pNN50; **Frequency-domain:** VLF, LF, HF, LF/HF; **Non-linear:** Poincaré plot (SD_1, SD_2, CSI).	Paired t-test Comparison of 5 minute intervals (in the range 15-0 min before onset) to interval 2h prior to onset.	MeanNN decreased moments prior to seizure onset, while LF/HF and CSI increased. Changes found for all seizures. Changes up to 30 minutes before onset, but most changes occur about 10 minutes before seizure onset.
Billeci et al. 2017 [78]	Short-term (30 minutes before onset) recordings. 13 patients.[2] Various types of epilepsy. Total 31 seizures.	**Time-domain:** MeanNN, NN50; **Frequency-domain:** LF_n[3], HF_n[3], LF/HF; **Non-linear:** Poincaré plot (SD_1, SD_2, CSI), RQA (Rec, Det, Lam, Ent, L_{max}, TT).	Friedman test + paired Wilcoxon test. Compare interictal (15 min), preictal (15 min) and ictal periods.	Significant changes between preictal and interictal periods: decrease in NN50, and increase in Ent and TT.
Gagliano et al. 2020 [24]	Short-term continuous recordings (10 minutes before onset). 9 patients with focal epilepsy.[2] Total 100 seizures.	**Time-domain:** MeanNN, SDNN, RMSSD, SDSD, NN50, pNN50.	k-means clustering (2 classes)	Significant differences between interictal and preictal periods. Changes start 3.5-6.5 minutes before seizure onset. Relation between seizure type and HRV pattern and preictal duration. Relation between seizure duration and preictal duration. Inter- and intra-patient variability.
Leal et al. 2021 [22]	4 hour long recordings from EPILEPSIAE database. 41 DRE patients with TLE. Total 238 seizures.	**Time-domain:** MeanNN, MinNN, MaxN, VarNN, SDNN, RMSSD, SDSD, NN50, pNN50; **Frequency-domain:** TP, VLF, LF, HF, LF_n[3], HF_n[3], LF/HF; **Non-linear:** Poincaré plot (SD_1, SD_2, SD_1/SD_2), DFA (α_1, α_2), ApEn, SampEn, LLE[4], CD[5], RQA (Rec, Det, Lam, Ent, L, L_{max}, TT).	Clustering (2 classes): k-means clustering, agglomerative hierarchical clustering, DBSCAN, expectation-maximization clustering.	Preictal solutions for 97/238 (41%) seizures. No solutions found for 4/41 patients. Preictal duration up to 120 min, but most often situated in the 40-0 min before seizure onset. Inter- and intra-patient variability. Time-domain features were more relevant.

[1]No information available about the duration of the recordings; [2]No information available about whether the dataset is constituted of DRE patients; [3]Normalized to account for inter-patient variability; [4]Largest Lyapunov exponent; [5]Correlation dimension.

There are some interesting aspects that should be highlighted from the analysis of the information in Table 3.4.

Dataset: The majority of the studies were conducted using relatively small datasets, both in number of patients and seizures. This can raise some questions as to the validity of their findings. Leal et al. [22] presented the most complete study in this regard, with the biggest dataset among the research papers analyzed. Additionally, only Behbahani et al. [71] and Leal et al. [22] used datasets composed of DRE patients.

Time analyzed: The preictal times analyzed by Billeci et al. [78] and Gagliano et al. [24] were also very short (15 and 10 min respectively). The results reported by Behbahani et al. [71] and Leal et al. [22] indicate that changes in HRV can be found much earlier before the seizure onset.

Feature extraction: The majority of studies used features from the three analysis domains discussed in Section 3.1.1. Only Gagliano et al. [24] used solely time-domain features. Additionally, there does not seem to be a consensus about the type of features which is better able to discriminate between preictal and interictal intervals.

Conclusions: Despite the limitations mentioned above, all of the studies analyzed found significant differences in HRV between the interictal and preictal intervals. These findings support the existence of the preictal period as a transitional period between normal and seizure brain activity. Lastly, it is important to emphasize that both Gagliano et al. [24] and Leal et al. [22] reported intra- and inter-patient variability in their findings, which reinforces the need for patient-specific approaches in seizure prediction.

3.2 Preictal Identification

Evidence of the preictal as a transition stage between normal and epileptic brain states has already been reported in the literature [13]. However, no consensus has yet been reached when it comes to its clinical definition, i.e., the characterization of patterns, duration and localization of the preictal in time. Furthermore, it has been reported that this period displays inter- and intra-patient variability [2, 22, 24].

In seizure prediction, correct preictal identification is crucial to obtain adequate and valid results. Hence, although some studies use a fixed preictal for the entirety

of the dataset, several researchers have performed attempts to determine the optimal preictal. This is usually done by applying a grid-search approach, where several preictals are used in the training phase and the one yielding the best performance results is chosen [2, 77]. However, this method is imprecise, computationally expensive and does not offer much insight into the mechanisms of seizure generation. Hence, there is a clear need for comprehensive studies focusing on finding patterns for preictal identification.

Bearing this in mind, and in an attempt to provide an alternative approach to the search for the optimal preictal, Leal et al. [22] proposed a method based on HRV and unsupervised learning (clustering). The study was based on the assumptions that (i) the preictal would be localized in the range of 120-0 minutes prior to the seizure, (ii) the solutions were comprised of two clusters, (iii) the smaller cluster would correspond to the preictal, and (iv) the preictal might not be continuous and/or located strictly before the onset of the seizure. Details about the dataset, features, and clustering algorithms used are available in Table 3.4.

The clustering algorithms were applied to combinations of three features, out of a total of thirty-two features. This process was conducted in a seizure-specific manner, and for all four clustering methods used. Afterwards, in the case where more than one acceptable solution was found, the optimal solution was selected based on time continuity and duration, i.e., solutions yielding continuous and longer preictals were favored. Figure 3.5 presents an example of the clustering solutions obtained for one patient.

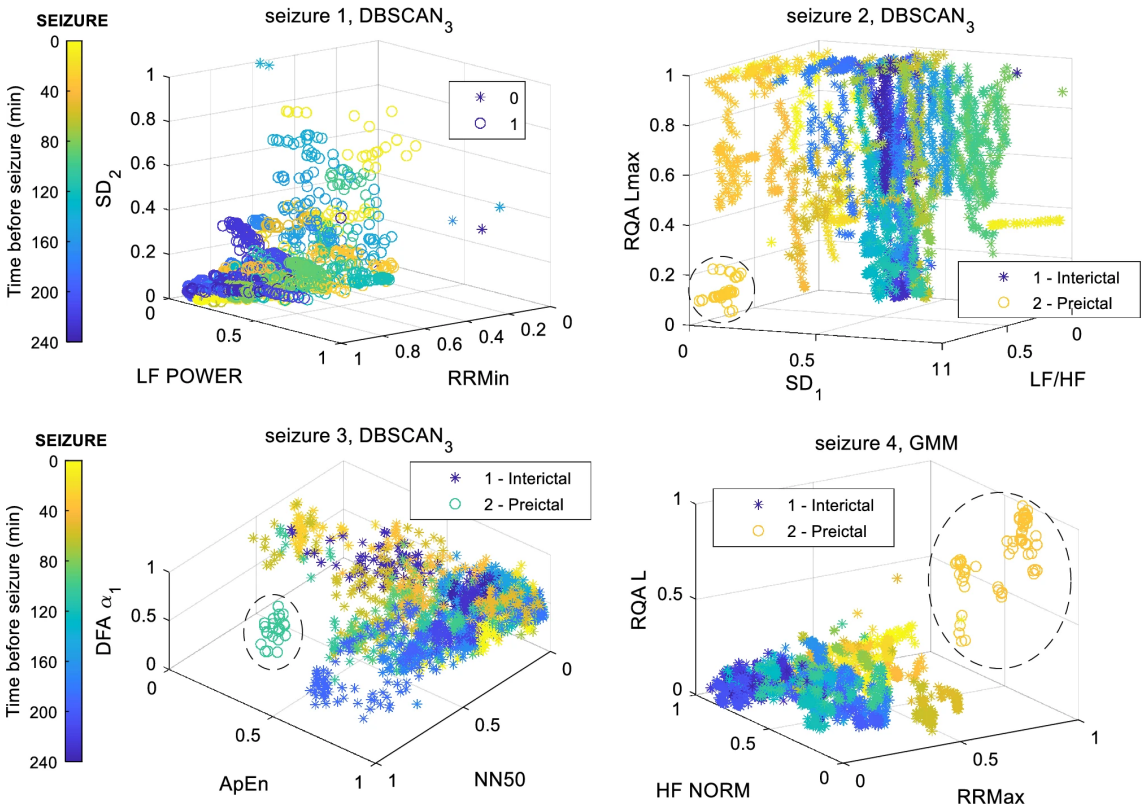


Figure 3.5: Clustering solutions obtained for patient 21902. The smaller clusters, inside the dashed black ellipses, represent the preictal solution. These are continuous for seizures 2 and 4, and discontinuous for seizure 3. No acceptable clustering solution was found for seizure 1. Source: Leal et al. 2021 [22]

Of the 238 seizures analyzed, it was possible to find solutions for 97 (41%). 52 (54%) of these solutions were continuous over time. Additionally, for 12 patients, solutions were found for more than half of the seizures considered. On the other hand, no solutions were found for any of the seizures of 4 of the 41 patients . A summary of the results obtained is presented in Figure 3.6.

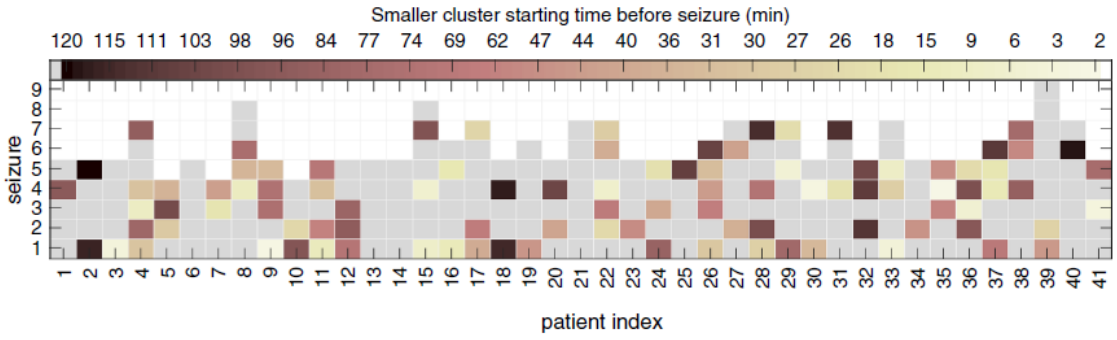


Figure 3.6: Summary of the accepted clustering solutions. Grey-coloured squares represent seizures without accepted clustering solutions. The x-axis represents the patient index, and the y-axis the seizure index. Source: Leal et al. 2021 [22]

Regarding the duration of the preictal clusters, they were found to range between 1.58 and 80.75 minutes. Additionally, after careful analysis of the duration of the preictal solutions, it was concluded that 53% of the solutions were located within 40-0 min before onset. The authors also concluded that time-domain features were predominant in the accepted solutions, namely RRMin, RRMean, and RRMax. This study presents interesting findings, which need to be validated, by incorporating them into a seizure prediction pipeline, in order to inspect if there are significant differences in performance, in comparison to the traditional grid-search approach.

3.3 Seizure Detection and Prediction

Epileptic seizure prediction started in 1975 with Viglione and Walsh [79]. Since then, many progresses have been made in the field of seizure detection and prediction, with the evolution of technology, storage and processing capacity allowing to perform faster analysis on larger quantities of data [10].

Seizure detection and prediction studies were typically based on EEG signals. This approach is the gold standard for epilepsy diagnosis, so it is reasonable that it is the most widely used signal for seizure detection and prediction. EEG signals can be acquired through scalp electrodes or, in a more invasive form, using intracranial electrodes. The latter are more practical for long-term usage and contain fewer artifacts [2]. Here, the NeuroVista study, conducted by Cook et al. [80], takes special relevance for being the first clinical trial of a seizure prediction device, and the only one to date. The trial was performed on a set of 15 DRE patients (9 male + 6 female, age = 44.5 $\pm$ 13.0 years). The system developed patient-specific algorithms in order to warn the patients of seizure likelihood, and achieved sensitivities in the range of 18-100% in the advisory phase. It was concluded that seizure prediction was feasible, and thus the foundations were set for advances in the field and their application in clinical practice. Unfortunately, the authors did not disclose information about the algorithms applied in the development of this system.

Besides the EEG signal, more recently, a plethora of signals and parameters have been analyzed as potential biomarkers for the prediction of seizures. Some examples of these signals are ECG, photoplethysmogram (PPG), accelerometry, electrodermal activity (EDA) and electromyogram (EMG). Additionally, multimodal techniques conjugating more than one signal have also been proposed, typically conjugating EEG and ECG [81–83].

Throughout the next subsection, the state of the art in seizure detection and

prediction using the ECG signal will be presented, while focusing on the most recent studies regarding seizure prediction based on HRV measures.

3.3.1 Seizure Detection and Prediction Based on Electrocardiogram (ECG)

In the past few years, the ECG signal has gained increased relevance in the field of seizure detection and prediction. In fact, this signal has proved useful in detection of seizures in newborns, since the clinical signs are typically too subtle to be noticed at this age and EEG use is difficult. However, great care should be taken when dealing with adult patients because the results might be severely influenced by confounding factors such as cardiac co-morbidities, stress, physical exercise, AED administration and circadian rhythms [15].

Some seizure detection and prediction studies based on the ECG signal with focus on HR have been developed with the aim of creating simple and interpretable systems. In a study by Osorio [84] published in 2014, seizures could be detected up to 0.8 seconds before onset. Ungureanu et al. [85] developed a patient-specific wearable system for detection of nocturnal seizures which achieved sensitivities of 95%. In 2017, De Cooman et al. [86] developed an online seizure detection system for TLE patients, obtaining sensitivity of 81.89% and FPR/h of 1.97 h^{-1}. Additionally, in 2018, De Cooman et al. [87] presented an adaptive seizure detection study based on real-time user feedback, achieving sensitivity of 77.12% and FPR/h of 1.24 h^{-1}.

Regarding HRV, several features can be extracted to evaluate cardiac function, as previously discussed in Section 3.1.1. As previously stated, the use of ECG-based information, more specifically HRV, to develop seizure detection and prediction models is relatively recent. Thus, the number of published research studies concerning these topics is still limited. In Table 3.5, a summary of recent HRV prediction and detection studies is presented, for easier comparison of the study typology (detection or prediction), dataset characteristics, methodology, and performance results.

Table 3.5: HRV-based seizure detection/prediction studies.

Authors	Typology	Dataset	Methodology					Results/Conclusions
			Feature Extraction	Feature Selection	Classification	Regular-ization	Statistical Validation	
Behbahani et al. 2014 [74]	Seizure detection	EPILEPSIAE database. Long-term continuous recordings. 15 DRE patients (8 male + 7 female, age = 42.2 ± 12.64 years) with focal epilepsy. Total of 206 seizures (96 FBTC + 110 FOIA).	**Time-domain:** MeanNN; **Frequency-domain:** LF, HF, LF/HF; **Non-linear:** Poincaré plot (SD_1, SD_2, SD_1/SD_2, S[6]).	-	ANNs (multi-layer perceptron) 75% data for training, 15% for validation and 15% for testing	-	-	FOIA seizures: Sensitivity = 83.33% Specificity = 86.11% FBTC seizures: Sensitivity = 86.66% Specificity = 90.00%
Behbahani et al. 2016 [88]	Seizure detection	EPILEPSIAE database.[1] 16 DRE patients (8 male + 8 female, age = 42.31 ± 11.89 years) with focal epilepsy. FOIA and FBTC seizures. Total of 170 seizures (86 left-sided + 84 right sided).	**Time-domain:** MeanNN; **Frequency-domain:** LF, HF, LF/HF; **Non-linear:** Poincaré plot (SD_1, SD_2, CSI).	-	SVM with RBF[7] kernel Leave-One-Out Cross-Validation	-	-	Right-sided seizures[4]: Accuracy = 86.74% Left-sided seizures[4]: Accuracy = 79.41%
Behbahani et al. 2016 [38]	Patient-specific seizure prediction SOP: various values between 1-8 min SPH: various values between 1-3.5 min	EPILEPSIAE database. Long-term (at least 4-6 days long) continuous recordings. 16 DRE patients (8 male + 8 female, age = 42.31 ± 11.89 years). Various types of epilepsy. Total of 170 seizures.	**Time-domain:** MeanNN; **Frequency-domain:** LF, HF, LF/HF; **Non-linear:** Poincaré plot (CSI).	Yes (un-specified)	Adaptive threshold (circadian rhythms - day and night)	-	Random predictor	Changes in features 30-15 minutes before onset. Sensitivity = 78.59% and FPR/h = 0.21 h^{-1} (with SPH = 110 s and SOP = 4 min 30 s). Performance above random predictor for 10/16 patients (with SOP = 2 min, SPH = 110 sec and FPR/h = 0.21 h^{-1}).

[1]No information available about the duration of the recordings; [2]No information available about whether the dataset is constituted of DRE patients; [3]Normalized to account for inter-patient variability; [4]No information about specificity or FPR/h; [5]TINN: Baseline width of the RRI histogram; [6]S: Area of the ellipse; [7]RBF: Radial Basis Function. [8]KFD: Katz Fractal Dimension.

Table 3.5: HRV-based seizure detection/prediction studies.

Authors	Typology	Dataset	Methodology					Results/Conclusions
			Feature Extraction	Feature Selection	Classification	Regular-ization	Statistical Validation	
Fujiwara et al. 2016 [89]	Seizure Prediction Preictal = 15 min	Long-term (24-72h) recordings. 14 DRE patients (10 male + 4 female, age 14-63 years). Various types of epilepsy. 11 awakening seizures + 4 sleeping seizures.	**Time-domain:** MeanNN, SDNN, RMSSD, TP, NN50; **Frequency-domain:** LF_n[3], HF_n[3], LF_n/HF_n[3].	-	Multivariate Statistical Process Control (MSPC)	-	-	Awakening seizures: Sensitivity = 91% FPR/h = 0.71 h^{-1} Sleeping seizures[4]: Sensitivity = 75%
Moridani et al. 2017 [77]	Patient-specific seizure prediction Preictal: grid-search with 5 min step (from 2h prior to onset).	PhysioNet database. 2 hour long continuous recordings. 7 patients with focal epilepsy[2]. Total 11 seizures.	**Time-domain:** MeanNN, SDNN, RMSSD, NN50, pNN50; **Frequency-domain:** VLF, LF, HF, LF/HF; **Non-linear:** Poincaré plot (SD_1, SD_2, CSI).	-	Threshold	-	-	Sensitivity = 88.3% Specificity = 86.2%
Pavei et al. 2017 [54]	Seizure prediction Preictal = 10 min	12 DRE patients (9 female + 3 male, age = 34.5 ± 7.5 years) with TLE[1]. Total 34 focal seizures.	**Time-domain:** SDNN, RMSSD; **Frequency-domain:** LF, HF; **Non-linear:** SampEn, Poincaré plot (CSI and CVI).	-	SVM with Gaussian kernel	-	-	CVI, CSI, SampEn and SDNN are potential biomarkers for seizure detection/prediction. Successful prediction of seizures up to 5 minutes before onset. Sensitivity = 94.1% FPR/h = 0.49 h^{-1}

[1]No information available about the duration of the recordings; [2]No information available about whether the dataset is constituted of DRE patients; [3]Normalized to account for inter-patient variability; [4]No information about specificity or FPR/h; [5]TINN: Baseline width of the RRI histogram; [6]S: Area of the ellipse; [7]RBF: Radial Basis Function. [8]KFD: Katz Fractal Dimension.

Table 3.5: HRV-based seizure detection/prediction studies.

Authors	Typology	Dataset	Methodology					Results/Conclusions
			Feature Extraction	Feature Selection	Classification	Regular-ization	Statistical Validation	
Billeci et al. 2018 [70]	Patient-specific seizure prediction Preictal = 15 min	Long-term recordings. 15 DRE patients (8 female + 7 male, age = 17.6 ± 9.9 years) with TLE. Most patients suffered from frontotemporal epilepsy. Total of 38 seizures. Seizures mostly recorded in awake state.	**Time-domain:** MeanNN, RMSSD, SDNN, NN50, PNN50, VarNN; **Frequency-domain:** LF_n[3], HF_n[3], LF_n/HF_n[3]; **Non-linear:** COSEn (Coefficient of Sample Entropy), KFD[8], Poincaré plot (SD_1, SD_2, CSI, CVI), RQA (Rec, Det, L_{max}, Lam, TT, Ent).	Stepwise regression analysis	SVM with RBF[7] kernel. Five-fold cross validation training. Additionally, for patients with 3 or more seizures, double cross-validation.	-	-	Five-fold cross validation: Sensitivity = 89,06% FPR/h = 0,41 h^{-1}. Double cross-validation: Sensitivity = 70.08% FPR/h = 3.36 h^{-1}. Average prediction time = 13.7 min. The recurrence plots related to the preictal phase were more organized when compared to ictal and postictal.
Giannakakis et al. 2019 [90]	Patient-specific seizure detection	Long-term (12-24h) recordings. 9 DRE pediatric patients (3 female + 6 male, age = 8.2 ± 4.3 years) with focal epilepsy. Total 42 focal seizures.	**Time-domain:** MeanNN, SDNN, RMSSD, NN50, PNN50, Triangular Index, TINN[5]; **Frequency-domain:** TP, LF, HF, LF/HF, LF_n, HF_n, LF_{peak}, HF_{peak}.	minimum Redun-dance Maximum Relevance (mRMR)	Threshold	-	-	Accuracy = 77.1% [4] Mean anticipation time = 21.8s
Yamakawa et al. 2020 [91]	Seizure prediction Preictal = 15 min	Same data used by Fujiwara et al. 2016 [89]. Selected 7 patients (4 female + 3 male, ages 9-54) with focal epilepsy. Total of 14 seizures.	**Time-domain:** MeanNN, SDNN, RMSSD, NN50, VarNN; **Frequency-domain:** TP, LF, HF, LF/HF.	-	Multivariate Statistical Process Control (MSPC)	-	-	Sensitivity = 85.7% FPR/h = 0.62 h^{-1}

[1]No information available about the duration of the recordings; [2]No information available about whether the dataset is constituted of DRE patients; [3]Normalized to account for inter-patient variability; [4]No information about specificity or FPR/h; [5]TINN: Baseline width of the RRI histogram; [6]S: Area of the ellipse; [7]RBF: Radial Basis Function. [8]KFD: Katz Fractal Dimension.

There are some important aspects to be discussed after the analysis of Table 3.5.

Preictal, SOP and SPH: Regarding seizure prediction studies, only Behbahani et al. [38] correctly applied the Seizure Prediction Characteristic (see Section 2.2.5), reporting the use of various values of SOP and SPH, even though it might be argued that the SPH durations are too short to allow proper measures to be taken (in open-loop systems). Fujiwara et al. [89], Pavei et al. [54], Billeci et al. [70] and Yamakawa et al. [91] defined a fixed preictal interval and deemed the prediction correct if the alarm was raised during that interval. In such cases, the preictal interval ranged between 10 and 15 minutes. These durations might be considered short if we take into account the results presented in Section 3.1.2. Additionally, only Moridani et al. [77] attempted to determine the optimal preictal duration by applying a grid-search approach, starting at 2 hours and advancing with a 5 minute step. However, the resulting preictal durations were not disclosed.

Typology: Concerning seizure prediction, three out of a total of six studies performed patient-specific analysis. When it comes to seizure detection, the ratio decreased to one out of three. It is important that studies are designed in a patient-specific manner as far as possible, since inter-patient variability has been reported in HRV dynamics (see Section 3.1.2).

Dataset: Most of the studies used datasets composed of relatively small numbers of patients and seizures, with the exception of Behbahani et al. [38, 74, 88], who used data from the EPILEPSIAE database. Additionally, most of the studies used long-term recordings, although the percentage who used continuous recordings was smaller. This might raise questions as to the validity of the results. Moreover, only Moridani et al. [77] did not specify the use of a dataset of DRE patients. While most studies included TLE patients, the only studies to research patients with this syndrome and report results for this specific group were Pavei et al. [54] and Billeci et al. [70].

Feature Extraction: All of the studies used linear time and frequency-domain features. The majority also used non-linear measures.

Feature Selection: Of the nine studies analyzed, only three performed feature selection. Besides lowering computational complexity, this step could be useful

to evaluate the discriminative capability of the features in identifying the preictal period, in order to gain further insight into the mechanisms of seizure generation.

Classification: The most commonly used classifiers were threshold-based and non-linear SVMs.

Regularization: None of the studies perform regularization to lower the number of false alarms, a step typically performed on EEG-based seizure prediction which could improve the performance of the models. Regularization methods used in the literature concerning other signals include the Firing Power [36] and the Kalman filter [92].

Performance Evaluation: Regarding performance evaluation, only one seizure prediction study (Moridani et al. [77]) did not report results in terms of sensitivity and FPR/h. It would be useful to understand whether researchers reported the latter in terms of the corrected FPR/h, to enable a fairer comparison of the results. However, only Billeci et al. [70] report that they did not use corrected FPR/h.

It should be highlighted that only Behbahani et al. [38] performed statistical validation, comparing the performance of the seizure prediction method to a random predictor. This step is crucial to ensure that the model is valid and performs above chance level. A more comprehensive description of statistical validation methods can be found in Section 2.2.7.

Results: All of the seizure prediction studies obtained sensitivities above 70% and, when computed, FPR/h was usually lower than 1 h^{-1}. In the case when FPR/h was not computed, specificity above 80% was reported.

3.3.2 Shortcomings of Seizure Detection and Prediction Studies

Current seizure detection and prediction systems display several shortcomings that hinder their clinical feasibility. Many authors present results with low reproducibility, and with satisfactory performance results only on previously selected data [2, 8]. Several limitations can be pointed out in current seizure prediction/detection methods:

- Use of features based on short-term, discontinuous recordings with low numbers of subjects and seizures [2, 8, 23];
- Lack of/inadequate statistical validation [2, 8];

- Testing models on data used for training [2];
- Not accounting for inter- and intra-patient variability [2, 8];
- Not taking into account confounding factors and concept drifts, such as circadian rhythms, stress and AED intake [8, 10, 49];
- Reporting performance metrics that are inadequate for imbalanced datasets (e.g. accuracy) [49];
- Determination of the preictal interval using a discrete grid-search approach.

Thus, a number of aspects need to be addressed and improved in further studies in order to make seizure detection/prediction feasible and potentiate the comparison of results between different researches. Algorithms should be designed in a patient-specific manner, based on long-term, continuous recordings with a significant number of seizures. The alterations in brain dynamics provoked by the practical aspects of signal acquisition in pre-surgical monitoring, where patients usually see their AED dosages decreased, should also be taken into account, as well as eventual concept drifts. Finally, performance evaluation should be conducted using the standard seizure prediction metrics, along with proper statistical validation, to ensure that the model performs better than chance and to enable comparison of results between studies [2].

4

Methodology

This Chapter describes the methodology adopted in this study. In Section 4.1, a brief overview of the proposed framework is presented. In Section 4.2, a description of the dataset is provided. In Sections 4.3 and 4.4, the basic steps of preprocessing and feature extraction, respectively, are described. In Sections 4.5, the process of splitting the data into train and test datasets is discussed. In Section 4.6, the ensemble learning method is briefly outlined. Sections 4.7, 4.8, 4.9, 4.10 and 4.11 are related to the labelling of the data samples, class balancing, definition of the preictal intervals, data standardization and feature selection, respectively. In Section 4.12, the choice of the classifier is briefly discussed. Section 4.13 is related to output regularization, and Section 4.14 to the training procedures, including the grid-search. Finally, Sections 4.15 and 4.16 describe the testing phase and the computation of performance metrics and statistical validation of the models.

Regarding the nomenclature, the term *clustering preictal* will be used herein to refer to preictal information obtained from the unsupervised learning study by Leal et al. [22].

4.1 Overview

The present work has been carried out with the main goal of exploring the impact of the consideration of the preictal period identified with unsupervised learning algorithms on seizure prediction performance. Toward that end, we developed patient-specific seizure prediction models based on Heart Rate Variability (HRV) analysis, integrating the preictal data obtained by Leal et al. [22] (see Section 3.2).

To determine whether the unsupervised preictal identification brings improvements to seizure prediction methodologies, two approaches were compared: the Standard approach and the Hybrid approach (see Figure 4.1). The Standard approach consists in applying the standard state-of-the-art grid-search to determine the optimal preictal interval. Here, instead of considering the same preictal interval

for all the seizures in the training phase, a seizure-specific analysis was used. The Hybrid approach defines the preictal interval based on the preictal unsupervised study by Leal et al. [22]. Thus, the model takes into account clustering preictal information for the seizures for which the preictal interval has been found in the unsupervised study, and performs grid-search on the remaining.

In both approaches, the Seizure Occurrence Period (SOP) was equal to the preictal period under analysis and the Seizure Prediction Horizon (SPH) was set to 10 minutes (see Section 2.2.5). In order to maintain the chronological organization, the first three seizures were selected for the training dataset, and the remaining for the testing dataset (see Section 4.5). This division assumes the existence of a temporal relation between seizures. Thus, the training and testing datasets comprise 123 and 115 seizures, respectively.

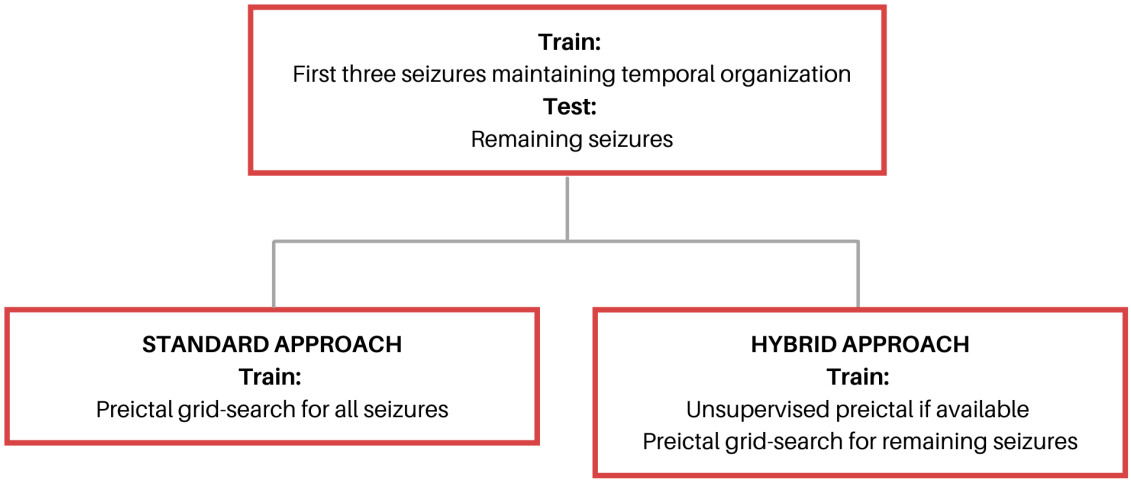


Figure 4.1: Schematic representation of the Standard and Hybrid approaches, designed to evaluate the impact of clustering preictals on seizure prediction performance. The aim is to compare the state-of-the-art approach with the proposed methodology coupling grid-search and the use of clustering preictal data.

The general seizure prediction framework applied in the present study is depicted in Figure 4.2. Since the proposed approach is patient-specific, the described steps were performed for each patient separately. In the previous study by Leal et al. [22], the raw Electrocardiogram (ECG) was preprocessed in order to extract HRV, and subsequently HRV features. Afterwards, clustering methods were applied in search of the preictal interval (see Section 3.2). The HRV feature dataset was used in this study, being divided into training and testing datasets. The training set was used to perform a grid-search to determine the optimal parameters and to train the

seizure prediction models using the optimized parameters. In the Hybrid approach, clustering preictal data is also considered in these steps. After the training phase, the models were applied to the testing dataset, with the aim of evaluating their capability of predicting upcoming seizures on unseen data. An ensemble learning approach was used in the training and testing phases. In the latter, the models' final output is post-processed in order to lower the number of false alarms, and finally, the performance is evaluated by computing the sensitivity and FPR/h and by comparison with the seizure-time surrogates statistical validation algorithm.

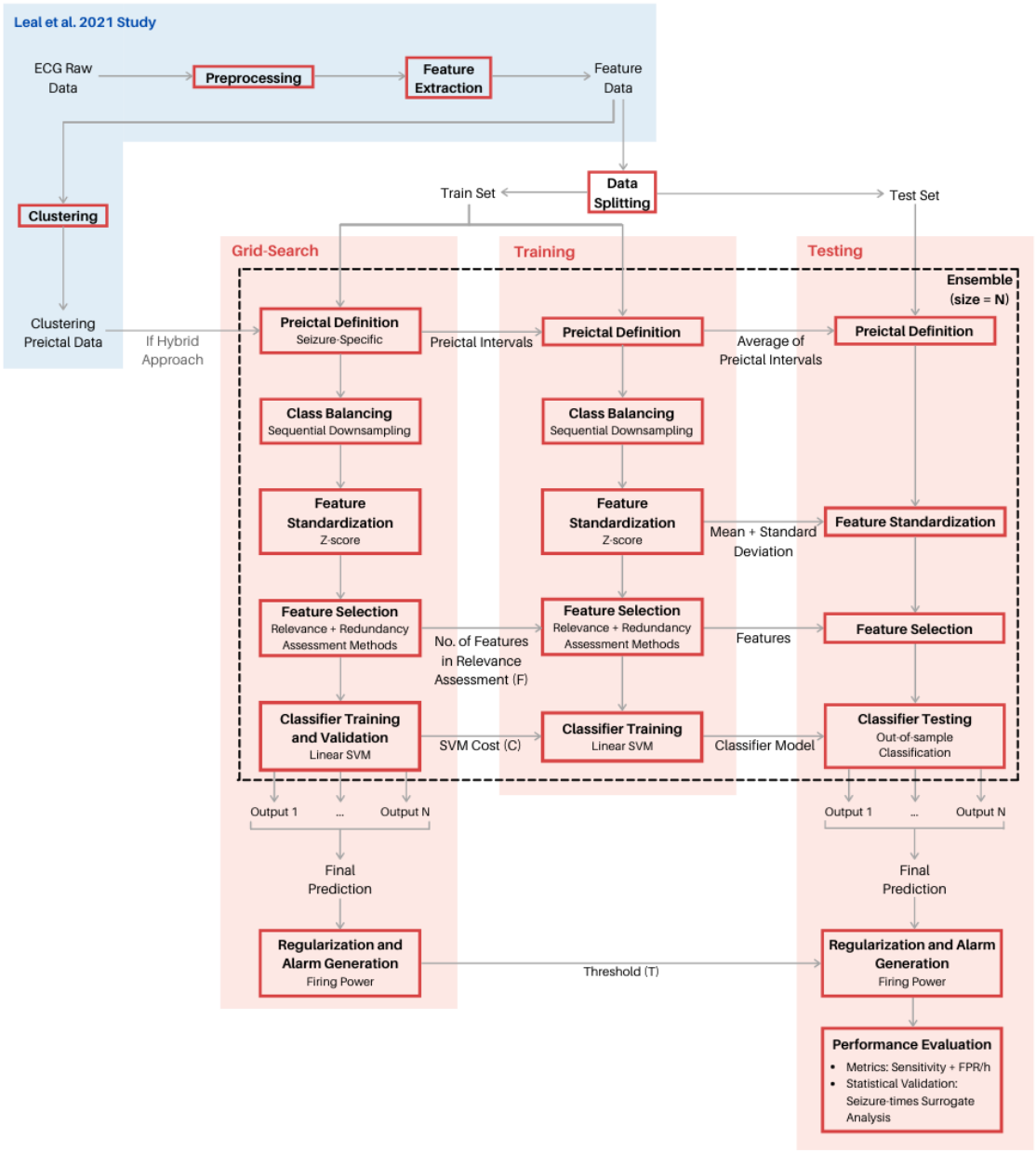


Figure 4.2: General framework of the proposed seizure prediction methodology.

4.2 Dataset Description

The dataset used in this study was extracted from the European Epilepsy Database, also known as EPILEPSIAE Database [1, 16]. This is the largest known epilepsy database, built as part of the FP7 EPILEPSIAE project, containing long-term continuous Electroencephalogram (EEG) and Electrocardiogram (ECG) recordings of 275 Drug Resistant Epilepsy (DRE) patients undergoing pre-surgical monitoring. The database also includes extensive clinical metadata (e.g., patient demographics, seizure type and vigilance state) and standardized annotations (e.g., seizure EEG and clinical onset).

The selected dataset consists of ECG data from 41 Temporal Lobe Epilepsy (TLE) patients (17 females and 24 males, aged 41 $\pm$ 16 years). This choice is largely based on the fact that disturbances in ANS cardiovascular control manifest predominantly in seizures originating in the temporal lobe (see Section 2.5). Metadata regarding the patients is presented in Table 4.1. The sampling rate for ECG acquisition was 256 Hz.

Only seizures separated by more than 240 minutes were considered independent, and thus the remaining were excluded from this study. After this selection, each patient had between four and nine seizures. The final dataset consisted of 238 seizures. Additionally, only the four hours preceding the onset of the seizure were considered.

Further information about the dataset can be consulted in Leal et al. 2021 [22].

Table 4.1: Dataset description

Patient	Gender	Age (years)	No. Seizures	Seizure Types	Seizure Pattern	Vigilance State
402	F	55	5	FOIA, FBTC, FOIA, FBTC, FOIA	t, t, t, t, t	A, A, A, A, A
8902	F	67	5	UC, FOIA, FOIA, FOIA, FOIA	a, b, a, m, a	A, A, A, A, A
11002	M	41	5	UC, FOIA, FOIA, FOIA, FOA	-, s, a, t, t	A, R, A, A, A
16202	F	46	7	UC, FBTC, UC, FOIA, FOIA, FOIA, FOIA	r, -, r, r, r, -, r	A, A, A, A, A, A, A
21902	M	47	4	UC, FOIA, FOIA, FOIA	t, t, t, b	A, A, A, R
23902	M	36	5	FOA, FOA, FOA, FOA, FOA	t, t, t, d, t	A, A, A, A, A
26102	M	65	4	FOIA, FOIA, FOIA, FOIA	m, t, t, t	A, A, A, A
30802	M	28	8	FOA, FOA, FOA, FOA, FOA, FOA, FOA, FOA	t, t, t, t, t, t, t, t	R, A, 2, A, A, R, 2, 2
32702	F	62	5	FOIA, FOIA, FOIA, FOIA, FOIA	t, t, t, r, a	A, A, A, A, A
45402	F	41	4	FOIA, FOIA, FOA, FOIA	t, t, t, t	A, A, A, A
46702	F	15	5	FOA, FOIA, FOIA, FBTC, FOIA	a, a, t, b, t	A, 2, A, 2, A
50802	M	43	5	FOIA, UC, UC, FOIA, FBTC	t, t, t, t, t	A, 2, 2, 2, A
52302	F	61	5	UC, FOA, UC, UC, UC	-, -, t, d, t	A, A, A, 1, A
53402	M	39	5	FOA, FOA, FOA, FOA, FOIA	-, -, -, -, t	A, A, 2, A, A
55202	F	17	8	FOIA, FOIA, FOA, UC, UC, FOA, UC, FOIA	t, d, t, t, t, r, r	A, A, A, A, A, A, A, A
56402	M	47	6	UC, UC, UC, UC, FBTC, FBTC	t, -, b, -, a, t	A, A, A, A, A, A
58602	M	32	7	FOIA, FOIA, FOIA, FOIA, FOIA, FOIA, FOIA	r, t, t, r, r, r, t	A, R, A, A, A, A, 2
59102	M	47	5	FOA, FOIA, FOIA, FOIA, FOA	-, t, t, t, t	A, A, A, A, A
60002	M	55	6	FOIA, FOIA, FOIA, UC, FOIA, FOIA	d, c, t, t, d, d	1, A, A, R, R, 1
64702	M	51	5	FOA, FBTC, FBTC, FBTC, FBTC	-, m, t, t, t	A, A, A, A, 2
75202	M	13	7	FOA, FOA, UC, FOA, FOA, FOA, FOA	t, t, t, t, t, -, t	2, 2, A, A, A, A, A
80702	F	22	7	FOIA, FOIA, UC, FOIA, UC, FBTC, FOIA	b, b, -, c, m, c, c	A, A, A, A, A, A, A
81102	M	41	5	FOIA, FOA, FOA, FOA, FOIA	t, t, t, t, t	A, A, A, A, A
85202	F	54	5	FOIA, FOIA, UC, UC, UC	m, c, m, m, m	2, A, A, A, A
93402	M	67	5	FBTC, FOIA, FOIA, UC, UC	t, t, t, t, t	2, 2, 2, 2, 2
93902	M	50	6	FOA, FOIA, FBTC, FOIA, FOIA, UC	t, t, d, d, d, d	A, A, 2, A, 2, A
94402	F	37	7	FOA, UC, FOIA, UC, FOA, UC, FOA	-, d, b, t, -, b, -	A, A, A, 2, A, 2, A
95202	F	50	7	FBTC, FOIA, FOIA, FOIA, UC, FOIA, UC	b, b, b, m, b, b, t	2, 2, 2, 2, 2, 2, 2
96002	M	58	7	FOIA, FOIA, FOIA, FOIA, UC, FOIA, FOIA	t, t, t, d, a, t, a	A, A, A, A, A, A, A
98102	M	36	5	FOA, UC, UC, UC, FBTC	-, -, -, -, -	A, A, A, A, A
98202	M	39	7	FOIA, FOIA, FOIA, FBTC, FOIA, FOIA, UC	t, a, t, t, t, t, t	A, A, A, A, A, A, A
101702	M	52	5	FOIA, FOIA, FOIA, FOIA, FOIA	t, t, t, r, t	A, A, A, 2, A
102202	M	17	7	FOA, UC, FOIA, UC, FOA, FOIA, UC	b, -, t, -, t, t, t	2, A, 2, A, A, 2, A
104602	F	17	5	FOIA, FBTC, FBTC, FBTC, UC	t, a, t, t, d	A, 2, 2, 2, 2
109502	M	50	5	FOIA, FOIA, FOIA, UC, UC	t, t, t, t, t	A, A, 1, A, A
110602	M	56	5	FOIA, FOIA, FOIA, FOIA, FOA	t, t, t, t, t	A, A, A, A, A
112802	M	52	6	UC, FOIA, UC, FOIA, FOIA, UC	t, t, t, t, t	A, A, A, A, A, A
113902	F	29	7	UC, FOIA, FOIA, FOIA, UC, UC, FOIA	t, d, t, t, t, t, t	A, A, 2, A, 2, A, A
114702	F	22	9	FOIA, FOIA, UC, FOIA, FOIA, FOIA, FOIA, FOIA, FOIA	t, t, t, t, d, t, t, d, t	A, A, A, A, A, A, 2, A, A
114902	F	16	7	FOA, FOIA, FOIA, FBTC, UC, FOIA, FOIA	s, b, s, t, r, a, t	A, A, A, 2, A, A, A
123902	F	25	5	FBTC, FBTC, FOIA, FOIA, FOA	t, t, t, t, t	2, 2, R, A, A

Gender: Female (F), Male (M); Seizure Type: Focal Onset Impaired Awareness, Focal to Bilateral Tonic-Clonic, Unclassified (UC), Focal Onset Aware; Seizure Pattern: rhythmic theta waves (t), rhythmic alpha waves (a), rhythmic beta waves (b), amplitude depression (m), rhythmic sharp waves (s), rhythmic delta waves (d), repetitive spiking (r), unclear(-); Vigilance State: Awake (A), REM sleep stage (R), Non-REM sleep stage I (1), Non-REM sleep stage II (2).

4.3 Extraction of HRV from the ECG signal

The extraction of HRV from the ECG signal performed by Leal et al. [22] will be briefly described bellow. The ECG recordings were firstly preprocessed and then the peak-to-peak intervals (R-R Interval) were computed. The different steps of this process are represented schematically in Figure 4.3.

The raw ECG data was inspected in each 5-min non-overlapping window. For each window, a notch filter was applied at 50 Hz to remove the powerline interference. Afterwards, the Discrete Wavelet Transform (DWT) was applied to remove baseline wander and obtain the frequencies of interest in the ECG [22].

The first step in R-R Interval series extraction is the identification of R-peaks. To that end, a modified Pan & Tompkins algorithm was applied to each 5-min non-overlapping window. Subsequently, the R-R Interval series was obtained by computing the time difference between successive R-peaks. This series was then edited to remove the interference of abnormal R-R Intervals. Finally, the signal was divided into 5-min windows with 98.33% (4min 55s) overlap [22]. At this point, the data is ready for feature extraction.

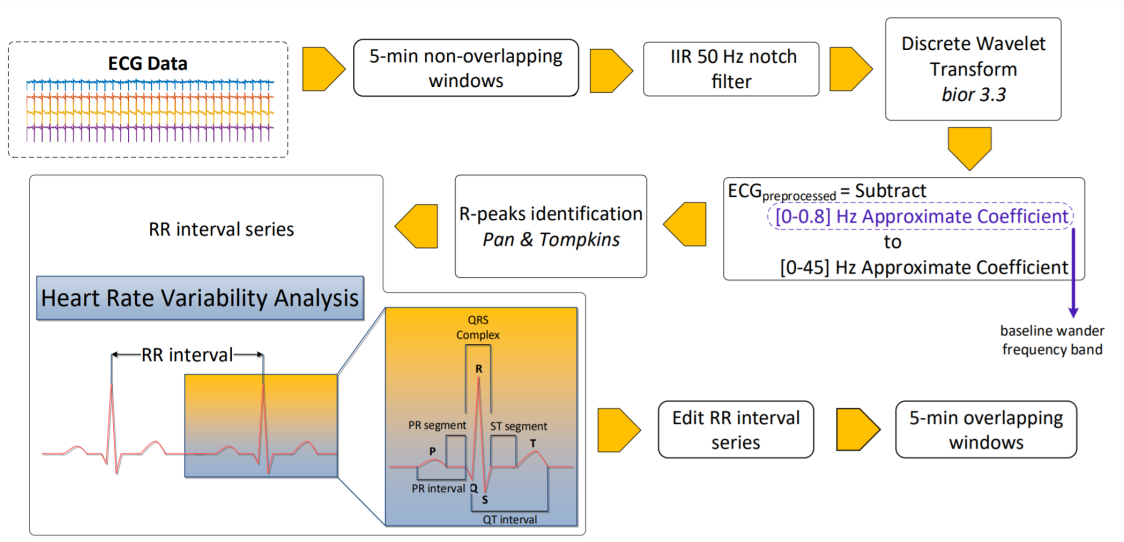


Figure 4.3: Schematic representation of ECG preprocessing and R-R Interval series extraction. Source: Leal et al. 2021 [22]

4.4 Feature Extraction

Several linear and non-linear HRV features in the time and frequency domains were extracted from the R-R Interval series in order to obtain information about the

relative balance between the sympathetic and parasympathetic nervous systems. In total, 32 features were extracted (see Table 4.2). The definition of the majority of the features and their relationship to the sympathovagal balance has been previously discussed in Section 3.1.1. Further information about the features can be consulted in Leal et al. 2021 [22].

Table 4.2: HRV features used in the study.

Linearity/Domain	Features
Linear/Time-domain	NN50, pNN05, SDNN, RMSSD, SDSD, RRMean, RRMin, RRMax, RRVar
Linear/Frequency-domain	Total Power, VLF Power, LF Power, HF Power, LF Norm, HF Norm, LF/HF
Nonlinear	SD_1, SD_2, SD_1/SD_2, DFA (α_1, α_2), ApEn, SampEn, LLE, CD RQA (Rec, L, TT, Det, Lam, Ent, L_{max})

4.5 Data Splitting

In order to perform training and testing, the dataset was split into two subsets for each patient (see Figure 4.4). The train set included the first three seizures in chronological order and was used for parameter optimization and model training. Thus, the train set may include seizures with and without clustering preictal information. The test set included the remaining seizures and was used to independently evaluate the previously trained models. This division aims to mimic a real-world scenario where the seizure prediction model is initially trained in a set of seizures that have been retrospectively collected, and is then applied to online data to predict imminent seizures and issue timely warnings.

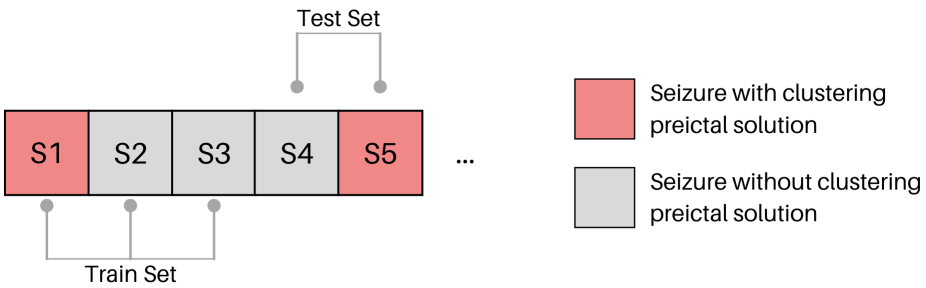


Figure 4.4: Schematic representation of the data splitting step. The seizures are organized in chronological order. The example is merely illustrative, as the total number of seizures and the seizures with clustering preictal data vary between patients.

4.6 Ensemble Learning

Ensemble learning was used to deal with the stochasticity of the class balancing process (see Section 4.9). This consists in repeating the training process N times, obtaining N classifier models. Afterwards, in the testing/validation phase, the final prediction results from the application of a voting scheme to the N prediction vectors (see Figure 4.5). In the present study, the ensemble size was N=31 to ensure that there is statistical significance and to avoid ties in the voting process. Regarding the voting scheme, a hard-voting approach was used, where, for each sample, the class with the most votes is chosen.

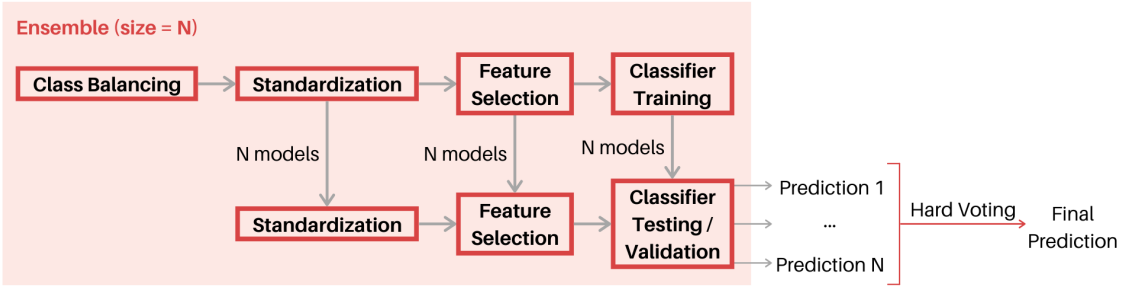


Figure 4.5: Schematic representation of the ensemble learning approach.

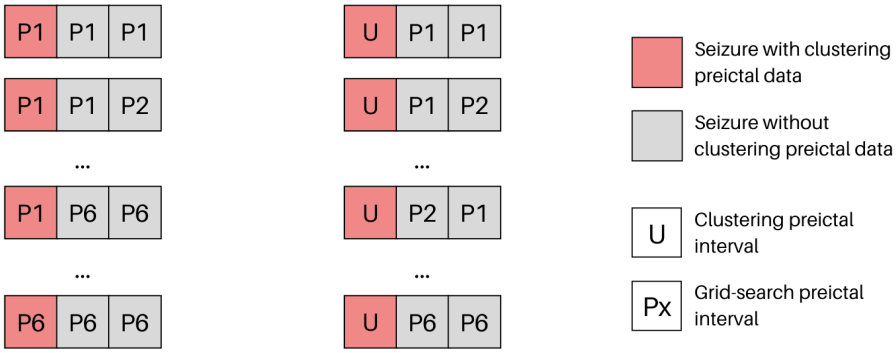
4.7 Data Labeling

The samples of each recording were labelled into three classes: interictal, preictal and SPH. The preictal starting time varied between seizures depending on the findings of the unsupervised learning or grid-search (see Section 4.8). We considered an SPH of 10 minutes in order to provide enough time for the patient or caregiver to take preventive action. The samples corresponding to the SPH were not fed to the classifier either in the training or testing phases.

4.8 Preictal Definition

In the training phase, the preictal intervals were defined using a seizure-specific approach (see Figure 4.6). In the Standard approach, the preictal intervals were defined based on the grid-search, by using permutations with repetitions of the six discrete values considered (see Section 4.14). In the Hybrid approach, we used the clustering preictals for the seizures for which clustering was conclusive and grid-search for the seizures with no clustering preictal information.

In the testing phase, the preictal interval was defined as the average of the preictal intervals obtained in the training phase (including clustering preictals, if available).



(a) Standard approach **(b)** Hybrid approach

Figure 4.6: Schematic representation of the preictal grid-search approach used in the training phase.

4.9 Class Balancing

As discussed in Section 2.2.8, class imbalance is a serious issue affecting the performance of seizure prediction models. In order to address this problem, we applied a random downsampling approach, in which the predominant class (interictal) is randomly undersampled in order to match the interictal and preictal number of samples.

The sequential downsampling approach is depicted in Figure 4.7. The process was carried out for each seizure independently, maintaining the chronology of the samples in each seizure episode. In sum, the interictal samples were divided into n groups, where n is the number of preictal samples. Afterwards, one sample was chosen randomly from each group. This way, samples from the entirety of the interictal interval were chosen, with the aim of preserving interictal representativeness.

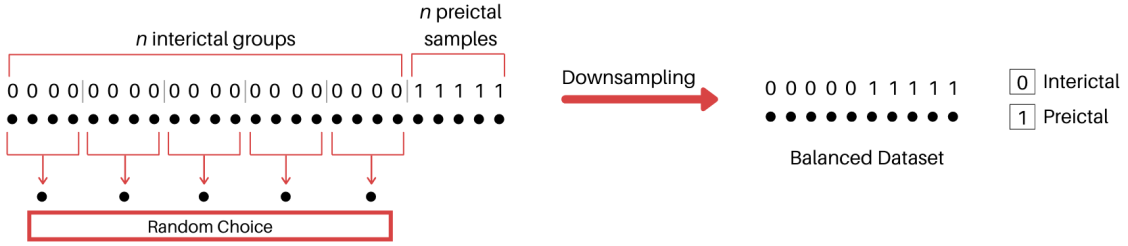


Figure 4.7: Schematic representation of the sequential downsampling process for one seizure. The samples are organized in chronological order.

4.10 Standardization

The feature data is standardized by subtracting the mean and scaling to unit variance (z-score normalization). Thus, we obtain N sets of mean and variance values during the training phase, which are used to scale the data in the testing phase.

4.11 Feature Selection

A feature selection step was applied to improve prediction by trying to select the most important features and to decrease computational complexity, potentially providing insight into the dynamics of seizure generation. To this end, both relevance and redundancy assessment methods were applied. Relevance methods evaluate the relationship of the feature data to the data labels in order to identify features which can better discriminate between interictal and preictal states. Redundancy methods simply evaluate the correlation between the features, removing features which do not provide additional information.

Relevance methods (described in Section 4.11.1) were first applied, followed by redundancy assessment methods (described in Section 4.11.2) (see Figure 4.8). The following methods of relevance assessment were applied: ANOVA F-value, Kruskal Wallis H-value, Area Under the Curve (AUC), and feature-target correlation. Redundancy methods consisted in applying Pearson's correlation coefficient (linear) and Spearman's rank coefficient (nonlinear) in parallel and selecting the features which were selected by at least one of the methods (union).

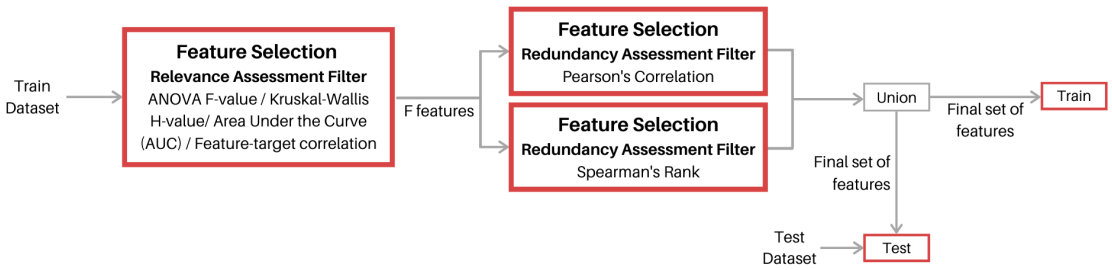


Figure 4.8: Schematic representation of the feature selection step. Firstly, F features are selected using one of the filter-based relevance assessment feature selection methods. Afterwards, redundancy-based methods are applied to the set of F features, yielding the final set of features.

4.11.1 Relevance Assessment Methods

We chose to use filter-based methods over wrapper-based due to their low computational cost on the long seizure prediction pipeline. The chosen methods, specified above, will be further discussed throughout the present section. Other methods were also tested, such as minimum Redundance Maximum Relevance (mRMR) [93] and mutual information, but were excluded because they were too computationally complex.

Preliminary experiments were also conducted with embedded methods, specifically Ridge [94] and Lasso [95]. However, it was not possible to apply these methods in the final computations. Ridge was computationally expensive, taking a long time to run the full training process. Lasso, on the other hand, did not converge even with a large number of maximum iterations.

For each method, we obtained a ranking of features, from which the F most relevant features were selected. The number of features chosen, F, was defined as either 10 or 20, considering that the total number of features is 32. The optimal value of F was defined by applying a grid-search approach (see Section 4.14). After the relevance assessment, redundancy assessment methods are applied to the set of F selected features.

Table 4.3: Brief description of the relevance assessment methods applied in this study.

Method	Description
ANOVA F-value	Selects features by ranking them according to the ANOVA f-statistics
Kruskal-Wallis H-value	Selects features by ranking them according to the Kruskal-Wallis h-statistics
AUC	Selects features by ranking them according to the Area Under the Curve (AUC)
Feature-target correlation	Selects features by ranking them according to the Pearson correlation to the target

4.11.2 Redundancy Assessment Methods

After applying relevance-based feature selection methods to select F features, redundancy assessment filter methods were applied. Thus, all the features selected by either the Pearson's correlation coefficient (linear) or the Spearman's rank coefficient (nonlinear) were selected. Initially, only features which had been selected by both methods were chosen, but this approach sometimes returned very few or even

no features.

We considered that features correlated by more than 90% were redundant. After evaluating pair-wise correlation between all features, we discarded the features of each pair that were more common among all pairs.

4.12 Classification

In order to select the best classifier, preliminary experiments were conducted using SVM with linear kernel and Logistic Regression. A linear kernel was chosen instead of non-linear kernels since similar results have been reported in the literature [96]. Additionally, linear SVMs are simpler and computationally lighter and require the optimization of only one parameter.

The results obtained using the two classifiers mentioned above showed no significant differences, and the Logistic Regression required more time to train. Additionally, SVMs have been widely used in the field of seizure prediction with good results [2]. Thus, the choice fell on the linear SVM.

As mentioned above, the linear SVM requires optimization of one hyperparameter, the cost (C). This is a regularization parameter used to define the penalization attributed to misclassifications as well as the width of the class separation margin. To select the optimal cost, a grid-search was performed (see Section 4.14).

4.13 Post-processing

After classification and voting, the obtained output consists of a point-by-point classification of the data. As it is highly unlikely that all points will be classified correctly, it is necessary to post-process this output in order to generate alarms that are well localized in time, thus reducing the number of noisy false alarms.

Therefore, we applied the regularization filter proposed by Teixeira et al. [36], known as firing power. This method quantifies the number of samples classified as preictal in a given window, called the *firing power* of the output. In order to do that, a moving window technique is used, where the length of the window corresponds to the number of samples of the preictal interval.

The mathematical formulation of this measure is given by

$$fp[n] = \frac{\sum_{k=n-\tau}^{n} o[k]}{\tau}, \tag{4.1}$$

where *fp[n]* is the firing power at the time n, τ is the number of samples of the moving window, and *o[k]* is the classifier output at time k.

The alarm generation process is depicted in Figure 4.9. In sum, the firing power at any given moment is calculated based on the past τ samples. The output measure is naturally normalized between zero and one, zero meaning that no samples in the interval were classified as preictal, and one meaning that all samples were classified as preictal. Finally, alarms are generated when the firing power exceeds a certain threshold value. The threshold is defined in a patient-specific manner in the grid-search (see Section 4.14).

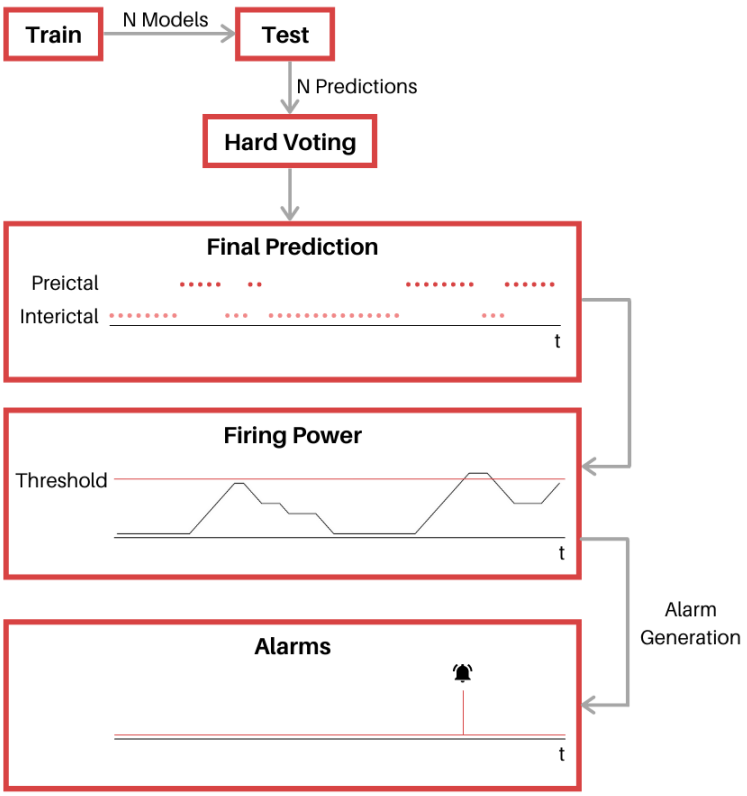


Figure 4.9: Schematic representation of the firing power regularization technique. The firing power is computed for the final prediction obtained by applying ensemble learning. When the firing power exceeds a defined threshold, alarms are generated. In this example, the length of the moving window is 6 samples and the threshold is 0.9.

4.14 Training Phase

Prior to training the models, a grid-search was used to search for the optimal problem parameters. This process incorporates the search for the best: number of features to select in the relevance assessment, SVM hyperparameter (cost), preictal

intervals, and firing power threshold. The values considered were the following:

- Number of features in the relevance analysis: F = [10, 20];
- SVM cost: C = [2^{-20}, 2^{-16}, 2^{-12}, 2^{-8}, 2^{-4}, 2^{-0}, 2^{4}, 2^{8}];
- Preictal intervals: P = [20, 40, 60, 80, 100, 120] minutes;
- Firing power threshold: T = [0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9].

The first step of the grid-search consists in optimizing the number of features in the relevance assessment, SVM cost and preictal locations. The optimization of the preictal intervals was described in Section 4.8. It should be highlighted that seizures with clustering preictal intervals starting after the SPH interval were not used in the training phase, since samples corresponding to the SPH are not fed into the classifier.

The number of preictal permutations is given by $PP = P^S$, where P is the number of preictal intervals considered in the grid-search and S is the number of seizures for which to determine the optimal preictal. Additionally, there are eight different options for the SVM cost (C) and two options for the number of features in the relevance assessment (F). Thus, the number of combinations of parameters (L) in the grid-search step in each study is presented in Table 4.4.

Table 4.4: Number of combinations of parameters assessed during the grid-search. This value depends on the number of seizures that require preictal optimization.

Approach	P	S	PP=P^S	C	F	L = PP · C · F
Standard	6	3	216	8	2	3456
Hybrid		1	6			96
		2	36			576
		3	216			3456

P: number of preictal intervals in the grid-search; S: number of seizures in the preictal grid-search; PP: number of preictal permutations in the grid-search; C: number of SVM cost values; F: number of number of features values in the relevance assessment; L: number of total combinations.

Similarly to Direito et al. [96], a k-fold cross-validation was used to optimize the parameters PP, C and F. The number of folds, k, corresponds to the number of training seizures (in our case k=3). This was combined with a performance evaluation metric (MM_{sample}) which incorporates sample sensitivity (SS_{sample}) and specificity (SP_{sample}). This metric translates the Euclidean distance between the point corresponding to these two values and the point corresponding to null performance ($SS_{sample} = 0$ and $SP_{sample} = 0$) in the ROC plot:

$$MM_{sample} = \sqrt{{SS_{sample}}^2 + {SP_{sample}}^2}. \tag{4.2}$$

The division in k groups (folds) is carried out by assigning one seizure to each fold. An example of this division is depicted in Figure 4.10. Each fold contains samples corresponding to both interictal and preictal periods. For each iteration i of the cross-validation procedure, the fold i corresponds to the validation set, and the remaining two folds correspond to the training set (see Figure 4.10).

Ensemble learning was also applied (see Sections 4.6 and 4.9). Thus, each of the k iterations was carried out N=31 times. To calculate the performance metric, MM_{sample}, the average of the performances over the N repetitions of the ensemble and the k folds of the cross-validation was computed.

Hereupon, the combination of parameters yielding the highest performance, i.e., highest MM_{sample}, was selected. If there was more than one combination of parameters yielding the highest performance, the one with the lowest runtime was selected.

Regarding the optimization of the firing power threshold, the first step consists in applying the hard voting approach to obtain the final prediction from the N prediction outputs corresponding to the highest performance. Afterwards, we computed the performance for each of the 17 threshold values considered when applying firing power. Specifically, we computed the sensitivity (SS) and FPR/h and then determined the Euclidean distance, D, between the point corresponding to these two values and the optimal performance point (SS=100% and FPR/h=0 h^{-1}) in the ROC plot [97, 98]:

$$D = \sqrt{(100 - SS)^2 + FPR/h^2}. \tag{4.3}$$

The threshold corresponding to the minimum distance was selected (see Figure 4.10).

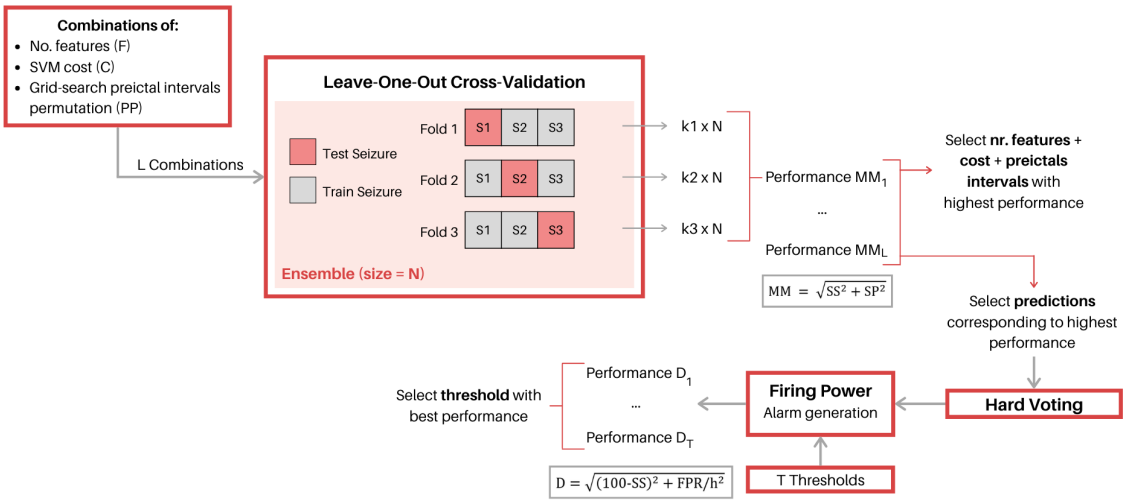


Figure 4.10: Schematic representation of the grid-search approach followed in the training phase for a given model.

After the grid-search, the final models are trained using the optimized preictal intervals and parameters (see Figure 4.2), yielding N models.

4.15 Out-of-sample Classification

Once completed the training phase, we obtain *N=31* optimized models, which are tested on an unseen dataset in the testing phase (see Section 4.5). Thus, the same steps applied in the training phase are applied in the testing phase, with the exception of the class balancing (see Figure 4.2).

The testing preictal interval corresponds to the average of the preictal intervals optimized during the training phase (see Section 4.8). The mean and standard deviation of each of the 31 training models' data were used to standardize the testing data 31 times (see Section 4.10), and the same features identified during feature selection in each of the 31 models were chosen for testing (see Section 4.11). Finally, the 31 classifier models were tested on this data, yielding 31 output vectors. In order to obtain the final prediction, the hard voting approach was used. Afterwards, the output was regularized using the firing power with the threshold defined in the grid-search. The last step corresponds to the performance evaluation.

4.16 Performance Evaluation

4.16.1 Performance Metrics

As discussed in Section 2.2.6, the performance of seizure prediction methodologies is evaluated based on two metrics: sensitivity and FPR/h. In the present study, the corrected FPR/h is used to account for the refractory period after an alarm is raised. The optimal values for sensitivity and FPR/h are 100% and 0 h^{-1}, respectively, corresponding to the scenario where all seizures are correctly predicted and no false alarms are raised.

4.16.2 Statistical Validation

The seizure prediction performance was also evaluated by comparison to the seizure-times surrogates (see Section 2.2.7.2).

The specific process of surrogate analysis used in this study is depicted in Figure 4.11. For each seizure, the preictal interval is randomly shifted to a different time in the preceding interictal period, this way obtaining the surrogate targets. Afterwards,

the surrogate sensitivity is calculated using the surrogate targets and the alarms obtained by testing the original targets.

This process is repeated R times. In the present study, R=30 to guarantee the statistical validity of the results. The distribution of surrogate sensitivities is then compared to the seizure prediction method's sensitivity. Since the process underlying the generation of surrogate sensitivities is random, we assume that these follow a normal distribution. Thus, a one-sample t-test was used.

A one-tailed test is applied to evaluate the null hypothesis that the performance of the seizure prediction methodology is not superior to the performance obtained with the surrogate predictor. Thus, the proposed methodology is said to achieve greater performance sensitivity than the surrogate predictor with statistical significance if the null hypothesis is rejected. Herein, a significance level of 5% was considered.

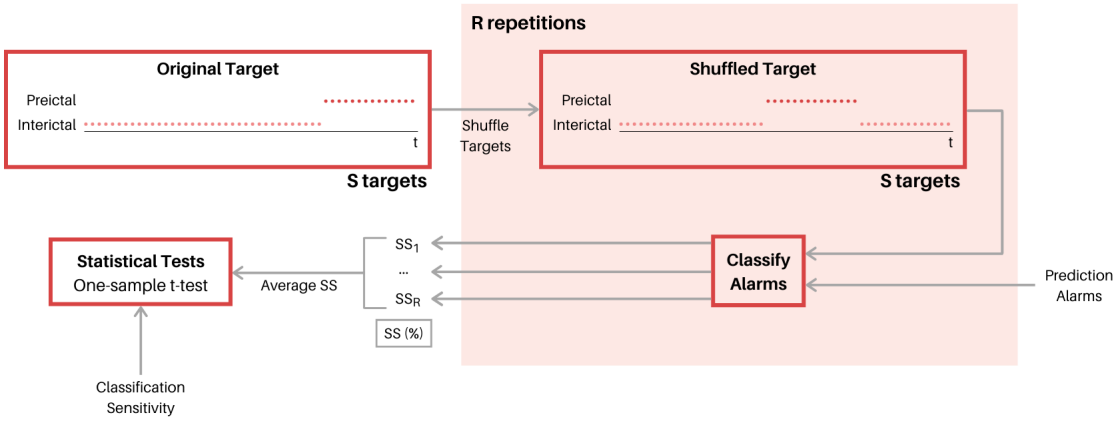


Figure 4.11: Schematic representation of the surrogate analysis. The process of shuffling is repeated separately for each seizure and the surrogate sensitivity is computed for each repetition. Here, R is the number of repetitions and S is the number of seizures. In this study, R=30.

5

Results and Discussion

In this Chapter, we present the results for the Standard and Hybrid approaches designed for selecting a preictal interval to integrate into supervised seizure prediction models. The Standard approach corresponds to the standard state-of-the-art approach, a seizure-specific grid-search of preictal intervals on a given range. The Hybrid approach integrates clustering preictals and grid-search preictals (applied for the seizures for which no clustering preictal has been found). We present the results for the training and testing phases of both approaches in Sections 5.1 and 5.2, respectively. In Section 5.3, we compare the seizure prediction performance between the Standard and the Hybrid approaches. Sections 5.4 and 5.5 contain the analysis of the starting time of preictal intervals and selected features, respectively. Afterwards, in Section 5.6 we compared the performance of Standard and Hybrid approaches to the state-of-the-art HRV- and EEG-based seizure prediction studies. In Section 5.7 we performed patient stratification into different groups based on the available metadata and observed the results obtained for both approaches in each group. Lastly, we performed a side study to visually validate the preictal intervals found on the HRV unsupervised learning study. Namely, we performed visual inspection of R-R Intervals and HRV features in search of alterations of their values over time, in trying to verify the source of the clustering preictal intervals (see Section A.3).

5.1 Training Phase

As previously explained in Chapter 4, the seizure prediction framework was applied using four feature selection methods: ANOVA F-test, Kruskal-Wallis H-test, Area Under the Curve (AUC), and feature-target correlation. Complete results, namely preictal interval, SVM cost, number of features selected during the relevance and redundancy assessment, and sample performance metrics, are presented in Appendix A, for the Standard approach (see Tables A.1, A.3, A.5, and A.7) and for the Hybrid approach (see Tables A.2, A.4, A.6, and A.8). Table 5.1 presents a

summary of the performance results obtained for each of the approaches and feature selection methods, in terms of mean and standard deviation of the sensitivity, specificity and the metric used to evaluate the k-fold cross-validation overall performance (see Section 4.14).

Table 5.1: k-fold cross-validation results (mean ± standard deviation) obtained for the Standard and Hybrid approaches and each feature selection method.

Feature Selection Method	Approach	$\mathbf{SS_{sample}}$	$\mathbf{SP_{sample}}$	$\mathbf{MM_{sample}}$
ANOVA F-test	Standard	0.54±0.29	0.74±0.18	1.05±0.05
	Hybrid	0.51±0.26	0.70±0.16	1.01±0.08
Kruskal-Wallis H-test	Standard	0.51±0.29	0.76±0.18	1.05±0.05
	Hybrid	0.51±0.26	0.70±0.16	1.02±0.07
AUC	Standard	0.42±0.32	0.83±0.15	1.03±0.05
	Hybrid	0.40±0.28	0.76±0.17	0.97±0.11
Feature-target correlation	Standard	0.37±0.30	0.82±0.17	0.99±0.13
	Hybrid	0.40±0.27	0.75±0.17	0.95±0.14

SS_{sample}: sample sensitivity; SP_{sample}: sample specificity; MM_{sample}: sample performance metric.

After inspecting the results in Table 5.1 we concluded that the average specificity values are higher than sensitivity for the two approaches and all feature selection methods. This means that the developed models are more successful in correctly classifying interictal than preictal samples. As mentioned previously in Section 2.2.6, there is a trade-off between these metrics, which means that one could obtain higher sensitivity values at the expense of lower specificity, and vice-versa, depending on the final application. In the present work, the aim was to maximize both metrics.

In addition, the standard deviations obtained were considerably larger than desired, especially when it comes to sensitivity. This high variability in the results indicates that, while high performance was obtained for some patients, very low values were obtained for others. This is not ideal, but further conclusions cannot be drawn without analyzing the test results, since high performance values in the training phase may result from data overfitting.

5.2 Testing Phase

Following the training phase, the machine learning models were tested on unseen data to evaluate their predictive power. We present the models' performance in terms of sensitivity and FPR/h. Additionally, we verified if the models performed

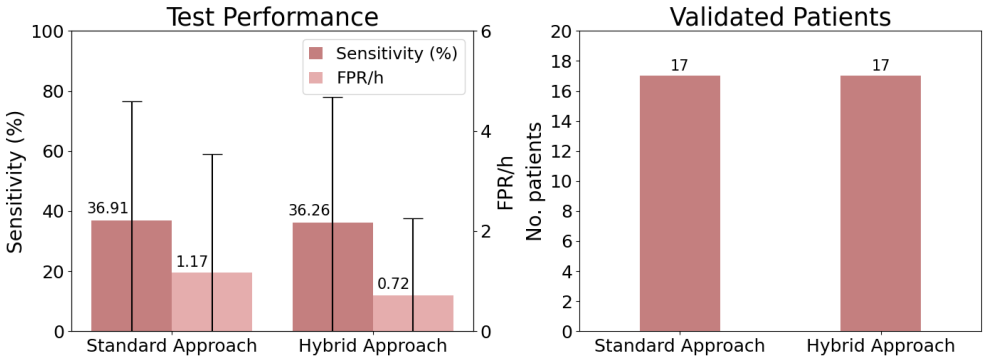
above chance level by running a statistical validation using the time-series surrogate analysis (See Section 2.2.7.2). A fixed SPH of 10 minutes was considered. The value of SOP corresponds to the testing preictal interval, therefore varying among patients. Complete results, namely preictal interval, firing power threshold, performance metrics, and surrogate analysis results, are presented in Appendix A, for the Standard approach (see Tables A.9, A.11, A.13 and A.15) and for the Hybrid approach (see Tables A.10, A.12, A.14, and A.16). The results obtained for each approach and each feature selection method are summarized in Figure 5.1.

Considering the average performance values presented in Figure 5.1, it can be concluded that the obtained sensitivities were suboptimal. As stated before in Section 2.2.6, patients with epilepsy require a seizure prediction system to yield sensitivities above 90% in order to have clinical utility [42]. Based on this, the average results obtained with both Standard and Hybrid approaches are far below this value. Regarding FPR/h, it has been suggested that patients undergoing pre-surgical monitoring (which is the case of our dataset) can have a maximum of 0.15 seizures per hour [25]. This value is admitted as the maximum FPR/h. Again, the average values fall short of the expectations, always exceeding this limit.

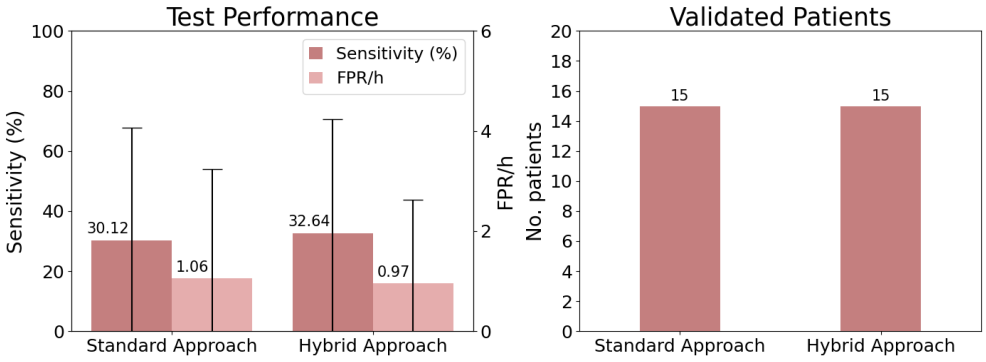
Regarding statistical validation, the percentage of patients validated in each study is usually around 40%, never reaching half of the dataset.

We can conclude that the average sensitivities are usually very similar in the Hybrid and Standard approaches when applying the same feature selection method, the only exception being with feature-target correlation feature selection. Average FPR/h values are always lower in the Hybrid approach, i.e., when clustering preictal information is used. Performing statistical validation on the developed models also returned similar results among the four feature selection methods.

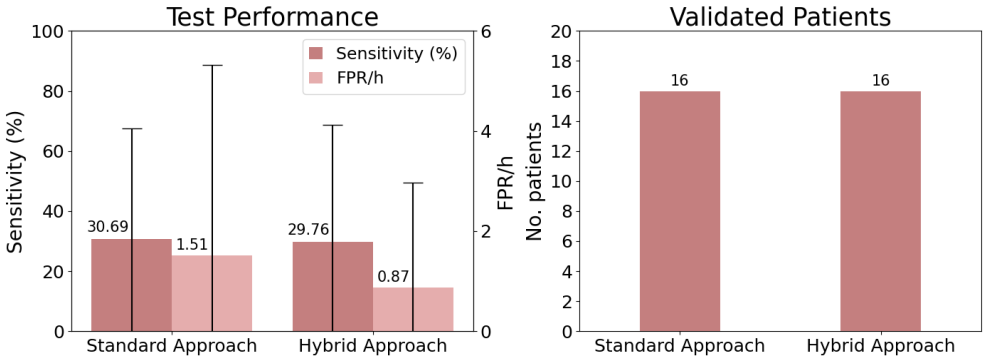
However, the results also show high variability, conveyed by the high standard deviation values. This indicates once again that while the algorithm performed poorly for some patients, satisfactory results were also obtained for others.



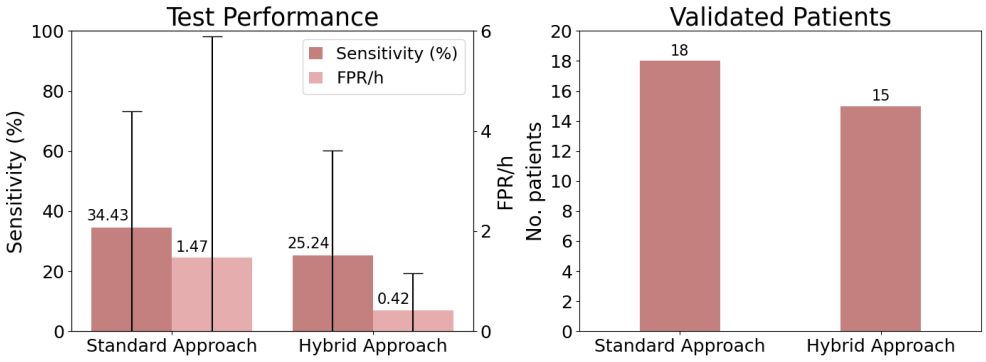
(a) ANOVA F-test



(b) Kruskal-Wallis H-test



(c) AUC



(d) Feature-target correlation

Figure 5.1: Comparison of test results (mean ± standard deviation) and number of patients validated with the surrogate analysis for the Standard and Hybrid approaches with different feature selection methods.

Figures 5.2 and 5.3 allow visualization and comparison of the sensitivity, FPR/h and statistical validation results for all patients among approaches and feature selection methods.

Concerning sensitivity, in Figure 5.2, it can be observed that there are a few cases in which the sensitivity exceeds 90%. In fact, in each approach, there are between 5 and 10 patients whose values exceed this limit. Furthermore, there is one patient (32702) for whom 100% sensitivity was obtained in all cases. However, there are many other cases when the sensitivity is null, and several patients (402, 26102, 81102, 94402, 98102) for whom we always obtained null values.

Regarding FPR/h, in Figure 5.3, we also observed that, for the same approach and feature selection method, there are cases with very high FPR/h, as well as several cases with zero false alarms raised. The number of patients verifying FPR/h below 0.15 h^{-1} lies between 16 and 22. However, the corresponding sensitivity values are usually low or null.

With regards to statistical validation, there are two patients (30802, 32702) for which the models perform above chance level across all approaches and feature selection methods, corresponding to approximately 5% of the dataset. Contrarily, performance above chance level was never obtained for five patients (12%).

Additionally, it was possible to obtain sensitivity above 100% and FPR/h below 0.15 h^{-1} for a few patients, namely patient 109502 in the Hybrid approach with ANOVA F-test and AUC feature selection, and in the Standard approach patient 53402 in with Kruskal-Wallis H-test feature selection and patient 21902 with feature-target correlation feature selection. Statistical validation revealed performance above chance in all four cases.

Due to the trade-off between sensitivity and FPR/h, it is not straightforward to state which of the methodologies used yielded the best performance results. This should be analyzed in light of the finality of the system, depending on the type of intervention for which it is designed. As previously mentioned in Section 2.2.6, higher values of FPR/h can be tolerated if the system applies closed-loop interventions, such as electrical stimulation, which do not produce serious side effects [15, 33, 39]. However, the SPH of 10 minutes used in this study is excessive for such interventions. Thus, the models developed in our study should only be considered for warning systems, and high FPR/h values cannot be tolerated since they increase the patient's anxiety levels and reduce confidence in the system.

Moreover, in order to evaluate the performance of the developed models, it is critical to determine if the inclusion of clustering preictal information produces improvements in seizure prediction performance.

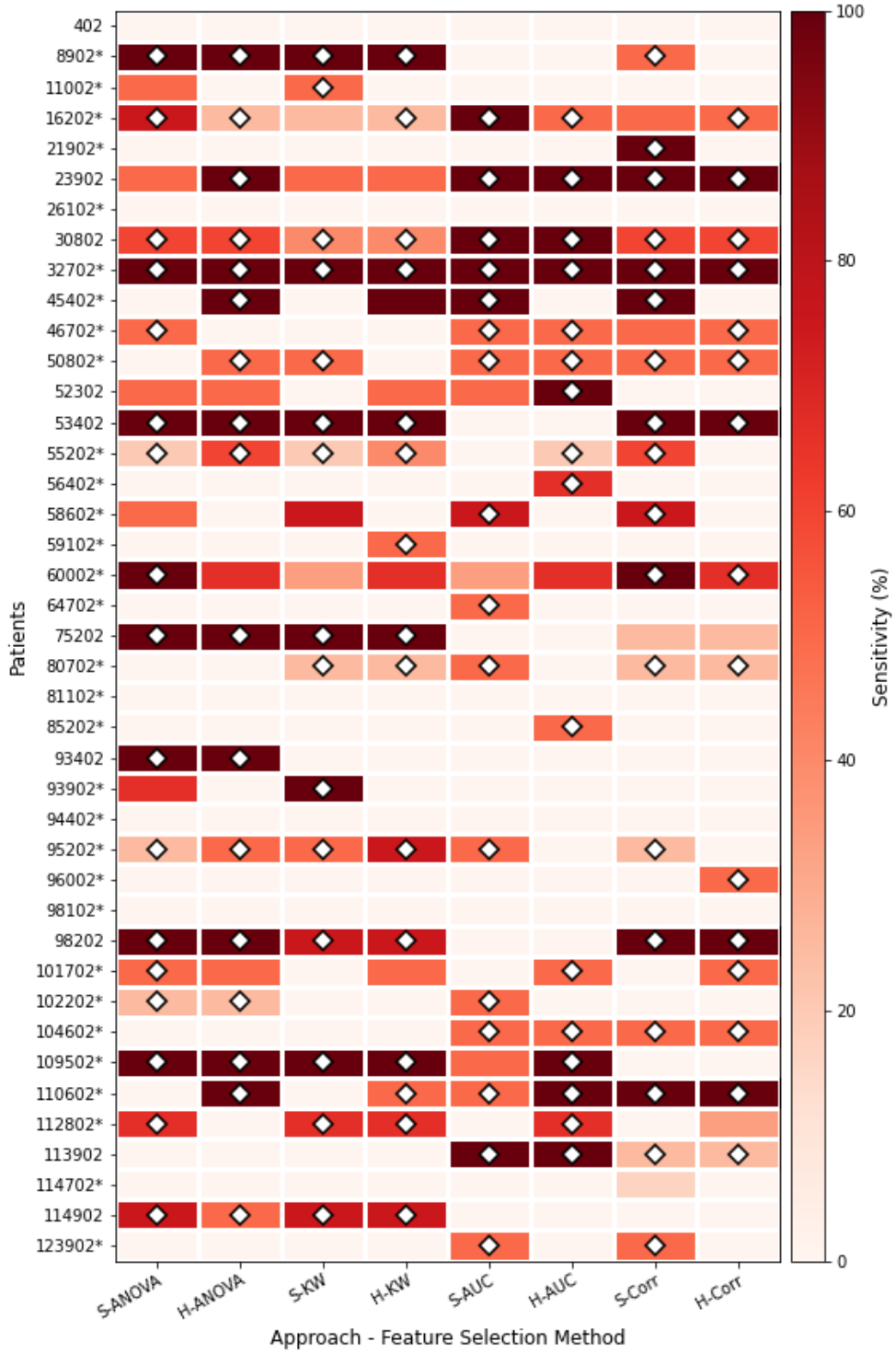


Figure 5.2: Sensitivity and statistical validation results of the seizure prediction algorithm for each of the approaches and feature selection methods. The red colour scale represents the sensitivity obtained for each patient in each case. The diamond indicates that the seizure prediction method performed above chance. The asterisk indicates patients with at least one accepted clustering preictal solution in the training set. S: Standard approach; H: Hybrid approach; KW: Kruskal-Wallis H-test; Corr: Feature-target correlation.

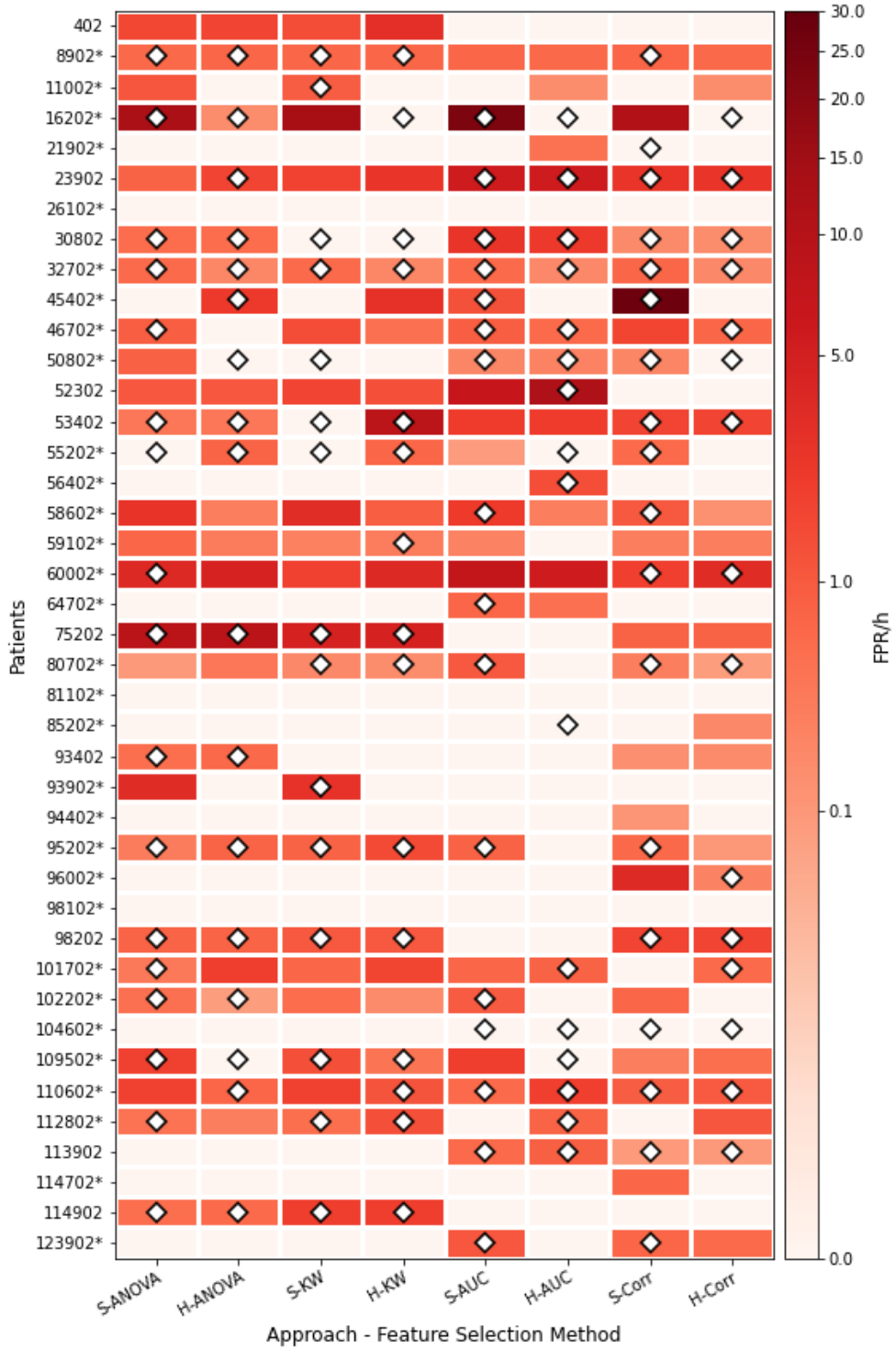


Figure 5.3: FPR/h and statistical validation results of the seizure prediction algorithm for each of the approaches and feature selection methods. The red colour scale represents the FPR/h obtained for each patient in each case. A non-linear scale was used to allow for a better analysis of the results. The diamond indicates that the seizure prediction method performed above chance. The asterisk indicates patients with at least one accepted clustering preictal solution in the training set. S: Standard approach; H: Hybrid approach; KW: Kruskal-Wallis H-test; Corr: Feature-target correlation.

5.3 Comparative Analysis

In order to compare the results obtained in the Standard and Hybrid approaches, computing the average of the performance metrics is not enough. It is necessary to compare the results' distribution of each approach using adequate statistical tests. Herein, a 5% confidence value was considered for all statistical tests.

The difference between both approaches lies in the fact that the Hybrid approach includes clustering preictal information. As such, we decided to analyse the statistical differences between Standard and Hybrid approaches using the patient's results for which clustering preictal intervals have been found for at least one of the three training seizures. This led to the exclusion of 10 patients: 402, 23902, 30802, 52302, 53402, 75202, 93402, 98202, 113902 and 114902. In sum, statistical differences between Standard and Hybrid approaches were assessed for 31 patients. We compared the prediction performance between both approaches for each feature selection method.

In order to choose the appropriate statistical test, the distributions were tested for normality using the Shapiro-Wilk normality test. The null-hypothesis of this test is that the distribution is normal. If the null-hypothesis is rejected for any of the distributions, non-parametric tests should be used. Otherwise, parametric tests are applied. Given that the p-value results (presented in Tables 5.2, 5.3, 5.4 and 5.5) are below the significance level of 5%, we rejected the null hypothesis that the Standard and Hybrid distributions come from a normal distribution. Thus, a non-parametric test for independent variables, the Mann-Whitney test, was used to compare the distributions. The null-hypothesis of this test is that the Standard and the Hybrid distributions come from the same distribution. The one-tailed Mann Whitney test was applied as we wanted to understand if using preictal clustering information (Hybrid approach) improves seizure prediction results, comparing to the Standard approach.

The present section reports the results obtained from this analysis. Figures 5.4, 5.5, 5.6, 5.7 display a visual representation of the data distributions for each feature selection method. Tables 5.2, 5.3, 5.4, 5.5 present the results of the statistical tests discussed above.

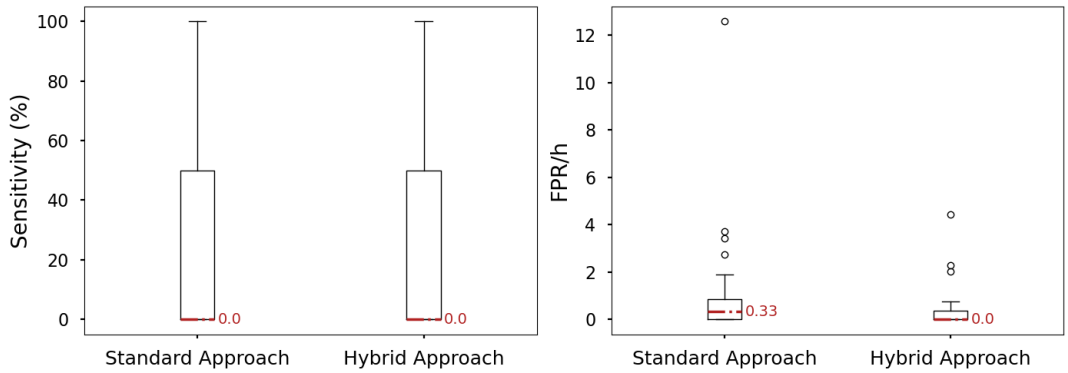


Figure 5.4: Boxplot data distributions of sensitivity and FPR/h for the Standard and Hybrid approaches with ANOVA F-test feature selection.

Table 5.2: Results of statistical tests conducted on the performance results obtained from the Standard and Hybrid approaches with ANOVA F-test feature selection.

Test	Approach	Sensitivity (%)		FPR/h	
		TS	p-value	TS	p-value
Shapiro-Wilk normality test	Standard	0.747	6.325×10^{-6}	0.476	2.073×10^{-9}
	Hybrid	0.691	8.629×10^{-7}	0.527	7.335×10^{-9}
Mann-Whitney U rank test	Standard vs. Hybrid	501.500	6.325×10^{-1}	565.000	1.031×10^{-1}

TS: Test Statistics.

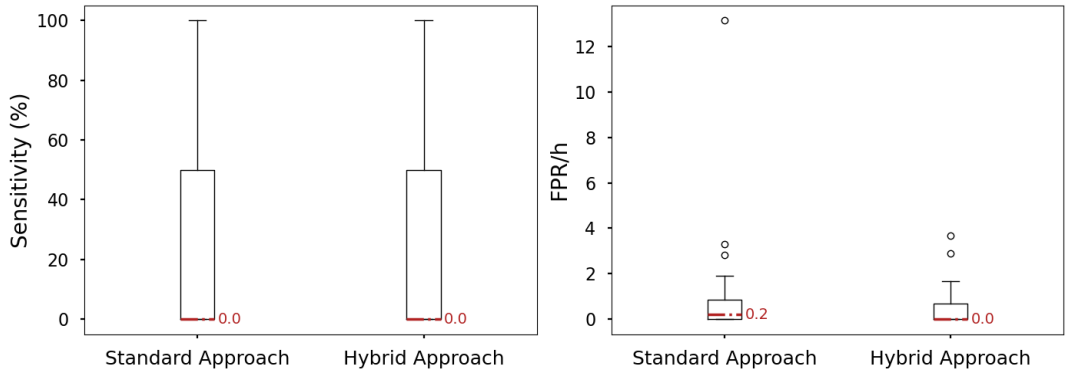


Figure 5.5: Boxplot data distributions of sensitivity and FPR/h for the Standard and Hybrid approaches with Kruskal-Wallis H-test feature selection.

Table 5.3: Results of statistical tests conducted on the performance results obtained from the Standard and Hybrid approaches with Kruskal-Wallis H-test feature selection.

Test	Approach	Sensitivity (%)		FPR/h	
		TS	p-value	TS	p-value
Shapiro-Wilk normality test	Standard	0.716	1.985×10^{-6}	0.432	7.365×10^{-10}
	Hybrid	0.730	3.628×10^{-6}	0.656	2.782×10^{-7}
Mann-Whitney U rank test	Standard vs. Hybrid	473.000	4.562×10^{-1}	520.000	2.786×10^{-1}

TS: Test Statistics.

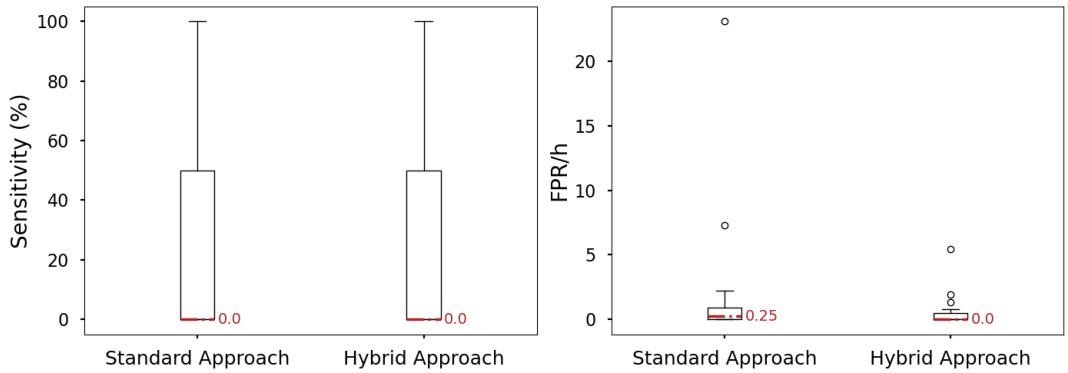


Figure 5.6: Boxplot data distributions of sensitivity and FPR/h for the Standard and Hybrid approaches with AUC feature selection.

Table 5.4: Results of statistical tests conducted on the performance results obtained from the Standard and Hybrid approaches with AUC feature selection.

Test	Approach	Sensitivity (%)		FPR/h	
		TS	p-value	TS	p-value
Shapiro-Wilk normality test	Standard	0.768	1.413×10^{-5}	0.346	1.168×10^{-10}
	Hybrid	0.736	4.143×10^{-6}	0.458	1.362×10^{-9}
Mann-Whitney U rank test	Standard vs. Hybrid	499.500	6.193×10^{-1}	593.000	4.594×10^{-2}

TS: Test Statistics.

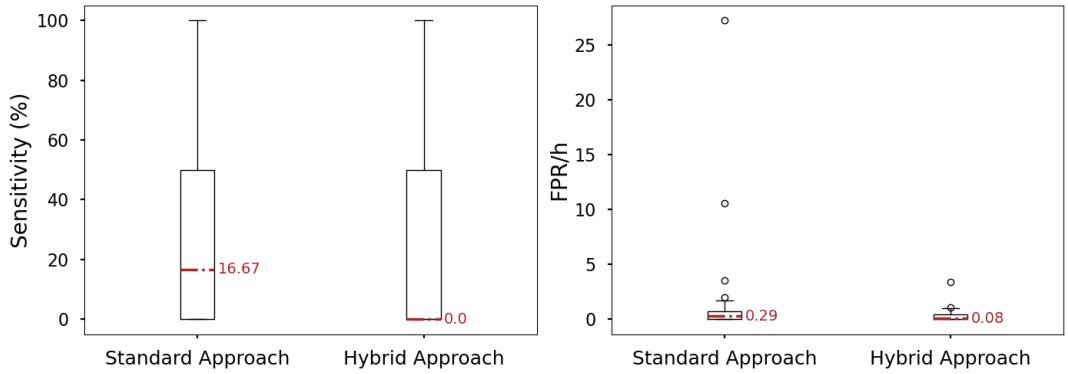


Figure 5.7: Boxplot data distributions of sensitivity and FPR/h for the Standard and Hybrid approaches with feature-target correlation feature selection.

Table 5.5: Results of statistical tests conducted on the performance results obtained from the Standard and Hybrid approaches with feature-target correlation feature selection.

Test	Approach	Sensitivity (%)		FPR/h	
		TS	p-value	TS	p-value
Shapiro-Wilk normality test	Standard	0.779	2.192×10^{-5}	0.352	1.334×10^{-10}
	Hybrid	0.686	7.365×10^{-7}	0.530	7.855×10^{-9}
Mann-Whitney U rank test	Standard vs. Hybrid	568.000	9.155×10^{-1}	594.000	4.837×10^{-2}

TS: Test Statistics.

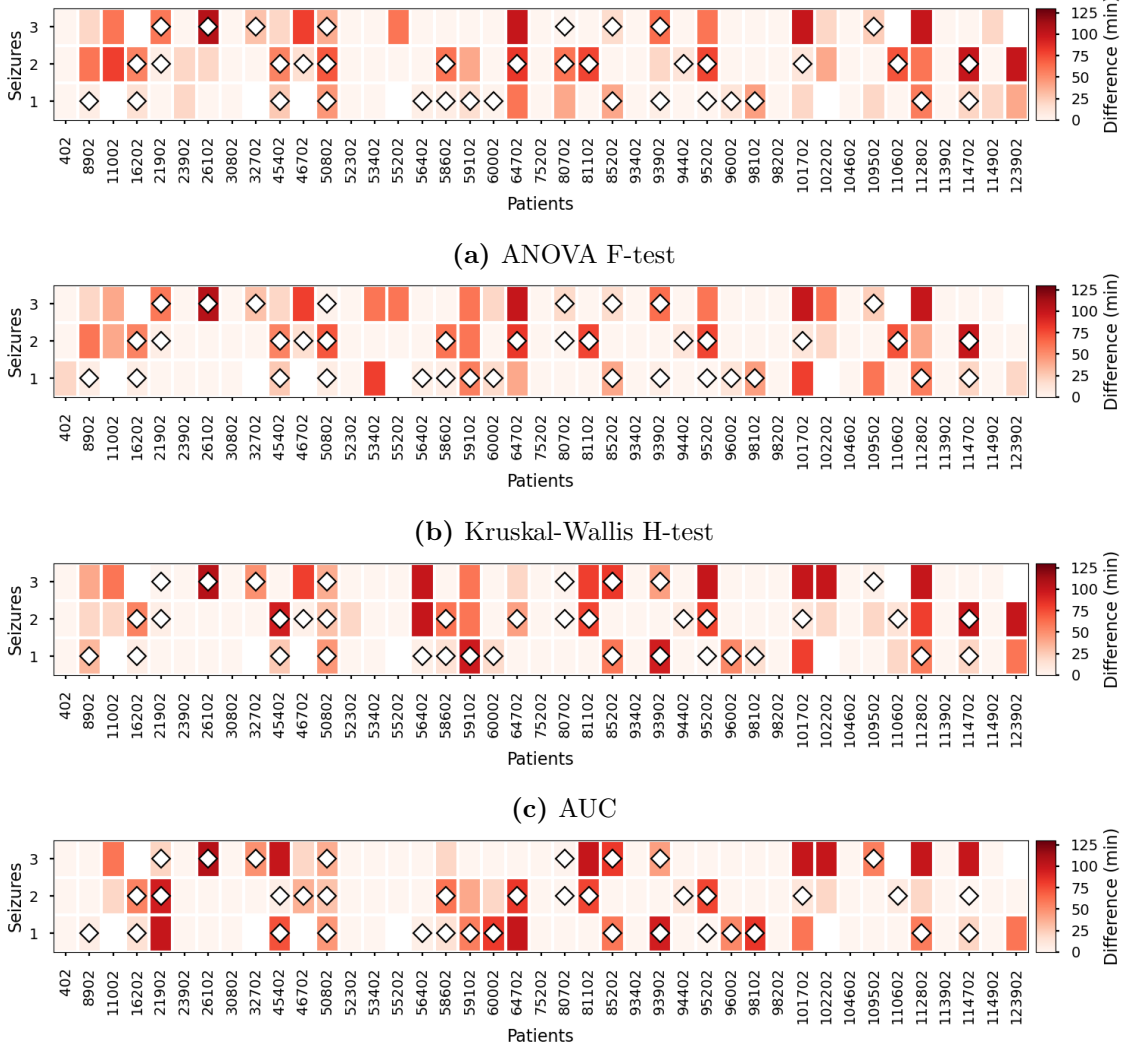
The results show statistically significant differences only for FPR/h distributions when using AUC and feature-target correlation feature selection. This denotes that, while the incorporation of preictal information does not yield better sensitivity, that is, does not allow the correct prediction of more seizures, it may provide lower FPR/h, in certain cases. Considering the discussion on the consequences of high FPR/h values in Section 2.2.6, this is highly beneficial for the patients. With lower FPR/h values, patients spend less time under false warning and thus, anxiety related to the alarms is reduced, allowing them to maintain confidence in the system.

5.4 Preictal Interval

To compare the preictal intervals obtained in the Standard and Hybrid approaches, we computed the difference between the preictal interval starting time found in both approaches, for each feature selection method (see Figure 5.8). Additionally, in order to better analyze the differences in the results obtained with the grid-search and those obtained by Leal et al. [22], we performed a separate analysis for the differences between the preictal interval starting time of seizures with accepted clustering preictal solution, and those without accepted solution (see Figure 5.9).

Regarding the results for the seizures for which no clustering solution was found, we were expecting that similar preictal intervals would be found in both Standard and Hybrid approaches, as both result from grid-search. In fact, the results presented in Figure 5.9 show that the median difference is null, which means that the resulting preictal intervals are usually the same. However, they also reveal some variability in the preictal starting time between both approaches. This variability is likely due to the stochasticity inherent to the process of class balancing performed during the training phase. Consequently, it might reflect the variability of the interictal ECG trace.

Considering, the results for seizures with clustering preictal solution, and comparing the results obtained with each of the feature selection methods, we concluded that ANOVA F-test and Kruskal-Wallis H-test presented the lowest differences between approaches. Hence, using these feature selection methods seems to lead to more coherent results for grid-search and clustering preictal intervals. In turn, we might hypothesize that the features selected by these two methods are the ones providing the preictal interval information in the unsupervised learning preictal search. In the next section, we tried to provide more insight on this matter.



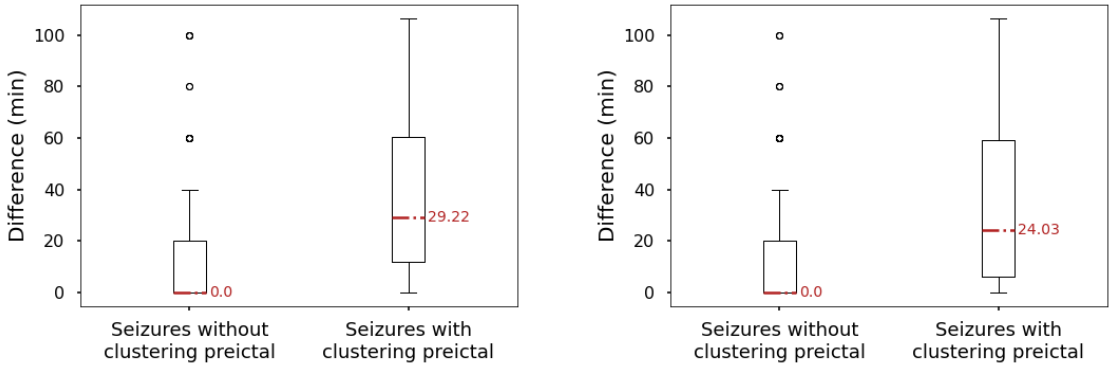
(a) ANOVA F-test

(b) Kruskal-Wallis H-test

(c) AUC

(d) Feature-target correlation

Figure 5.8: Differences between preictals used in the Standard and Hybrid approaches, for each feature selection method. Seizures marked with a diamond were trained using the clustering preictal information. White blocks are related to seizures with clustering preictal interval starting after the SPH, which were therefore not used for training in the Hybrid approach.



(a) ANOVA F-test

(b) Kruskal-Wallis H-test

(c) AUC

(d) Feature-target correlation

Figure 5.9: Boxplot data distributions of the difference between preictal intervals in the Standard and Hybrid approaches, for each feature selection method. The values are separated into differences in seizures with accepted clustering preictal solution, and differences in seizures without accepted solution.

5.5 Feature Selection

In this section, we inspected the results of feature selection for each of the four methods and each seizure prediction approach (see Section 4.11). In Figures 5.10 and 5.11, we present the relative frequency of each feature in the 31 models obtained in the training phase, after the application of relevance and redundancy assessment methods, for the Standard and Hybrid approaches, respectively. Importantly, we noticed that in the grid-search to optimize the number of features to select in the relevance assessment (see Section 4.14), F=10 was selected slightly more often than F=20.

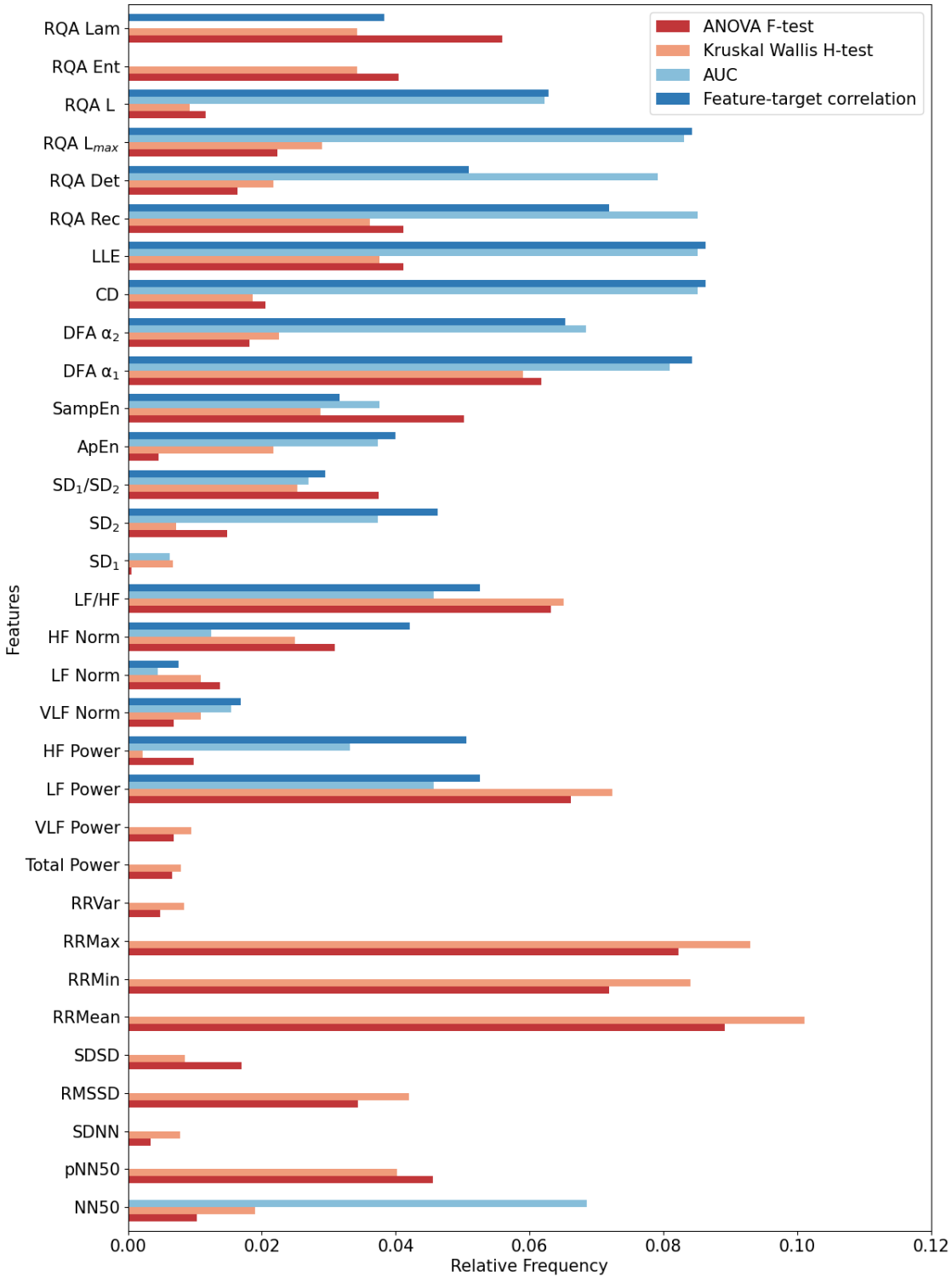


Figure 5.10: Bar graph of the relative frequency of selection of each feature depending on the feature selection method used, in the Standard approach.

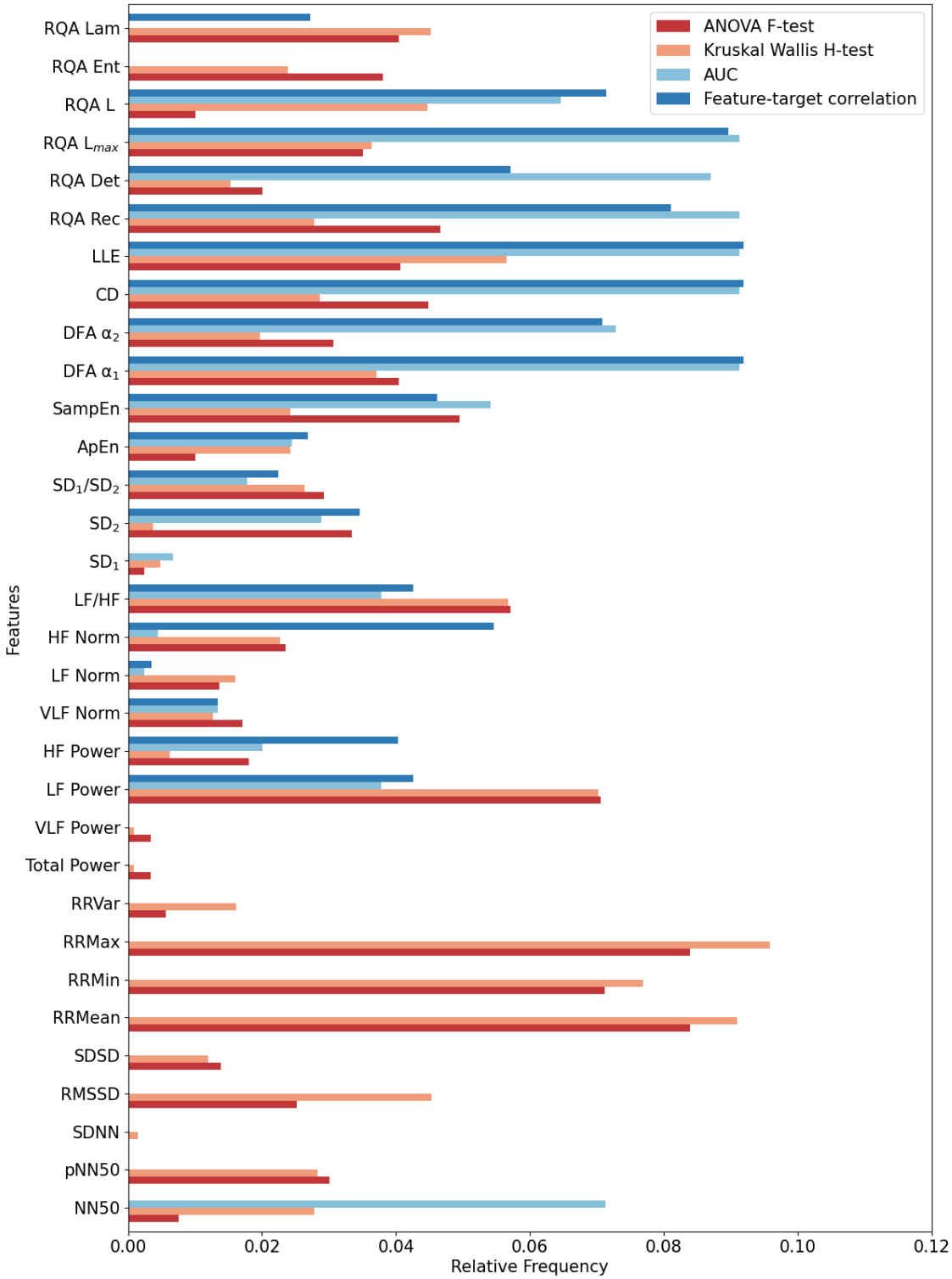


Figure 5.11: Bar graph of the relative frequency of selection of each feature depending on the feature selection method used, in the Hybrid approach

Results indicate that feature selection yields similar results among Standard and Hybrid approaches. Nevertheless, we noticed clear differences in the features selected by ANOVA F-test and Kruskal Wallis H-test methods, when comparing to AUC and target-feature correlation, in both approaches. Typically, when using the latter, the time-domain linear features are not selected for the final model. Non-linear features are prevalent when using these two methods. Contrarily, ANOVA F-test and Kruskal Wallis H-test methods frequently select features such as RRMin, RRMean, RRMax, LF/HF and LF Power. These results are in line with the previous findings regarding the preictal starting time differences found among the feature selection methods. Since ANOVA F-test and Kruskal Wallis H-test methods select the features that most frequently led to the identification of unsupervised learning preictals, it is natural that fewer differences are seen among Standard and Hybrid preictal intervals. Consequently, this means that similar preictal intervals are used by both approaches and therefore no statistically significant differences exist among the final performance observed for Standard and Hybrid approaches.

Furthermore, there are certain features which were seldom selected, suggesting that they do not provide new and relevant information for seizure prediction. This is the case of SD_1, LF Norm, VLF Norm, VLF Power, Total Power, RRVar and SDNN.

5.6 Comparative Analysis with Other Studies

In this section, we compare our results with those obtained in other state-of-the-art HRV-based seizure prediction studies (see section 3.3.1), as well as with other seizure prediction methodologies based on EEG. Both comparisons will be performed.

The dataset used in our study includes uniquely TLE patients, due to the close proximity between the temporal lobe and anatomical structures involved in autonomic control, which determines that alterations in ANS function are predominant in seizures originating in the temporal lobe [63] (see Section 2.5). Thus, this comparison will focus on studies including TLE patients.

It is important to note that comparing our models with state-of-the-art seizure prediction models can be challenging due to differences in the explored datasets as well as in the methodologies employed. Characteristics such as the number of patients, type of epilepsy (e.g. temporal lobe epilepsy), the post-processing techniques, the choice of SOP and SPH, and the statistical validation method may explain the differences in the final results reported in each study.

5.6.1 Comparative Analysis with Heart Rate Variability (HRV) Studies

Firstly, we compare our models with state-of-the-art HRV-based seizure prediction models (see Table 3.5) including Temporal Lobe Epilepsy patients from various databases. Table 5.6 shows the results of the present study and the HRV-based studies complying with the aforementioned criteria.

Table 5.6: Results obtained in the present study and state-of-the-art HRV-based studies.

Study	No. TLE Patients	Sensitivity (%)	FPR/h	Patients Validated (%)
Behbahani et al. 2016 [38]	12	77.09	0.21	70
Fujiwara et al. 2016 [89]	8	N.A.	0.72	N.A.
Pavei et al. 2017 [54]	12	94.1	0.49	N.A.
Billeci et al. 2018 [70]	15	89.06	0.41	N.A.
This study (ANOVA F-test, Standard approach)	41	36.91	1.17	41.5
This study (ANOVA F-test, Hybrid approach)	41	36.26	0.72	41.5
This study (Kruskal-Wallis H-test, Standard approach)	41	30.12	1.06	36.6
This study (Kruskal-Wallis H-test, Hybrid approach)	41	32.64	0.97	36.6
This study (AUC, Standard approach)	41	30.69	1.51	39.0
This study (AUC, Hybrid approach)	41	29.76	0.87	39.0
This study (Feature-target correlation, Standard approach)	41	34.43	1.47	43.9
This study (Feature-target correlation, Hybrid approach)	41	25.24	0.42	36.6

In Behbahani et al. [38], a sensitivity of 77.09% was obtained for TLE patients, with a fixed FPR/h of 0.21 h^{-1} and after optimization of SOP and SPH for each patient. This average sensitivity value largely surpasses the values obtained in this study. Additionally, statistical validation was performed by comparison to the random predictor, revealing performance above chance for 70% of the TLE patients, when using SOP = 2 min and SPH = 110 s. This is a considerably higher percentage when compared to our results.

In a study with patients with various epilepsy syndromes, Fujiwara et al. [89] reported an overall sensitivity of 91%, but did not specify the value for the TLE patients. Regarding FPR/h, the authors reported an average of 0.72 false alarms

per hour for TLE patients. In our study, two approaches achieved lower or equal FPR/h (ANOVA F-test and Feature-target correlation, Hybrid approach). However, without knowledge of the sensitivity, it is impossible to perform a fair comparison since low values of FPR/h may be obtained at the expense of lower sensitivity. No statistical validation was conducted.

Pavei et al. [54] reported average sensitivity of 94.1% and FPR/h of 0.49 h^{-1}, thus achieving higher performance than any of the approaches considered in this study. However, no statistical validation was performed.

Billeci et al. [70] reported 89.06% sensitivity and FPR/h of 0.41 h^{-1}, thus achieving higher performance than our models. However, no statistical validation was carried out.

As stated above, there are several characteristics of the seizure prediction methodology which can affect the seizure prediction performance. Behbahani et al. [38] reported the only seizure prediction study which used data from the EPILEPSIAE database. When it comes to classification, Pavei et al. [54] and Billeci et al. [70] applied SVMs, although with non-linear kernels. Behbahani et al. [38] and Fujiwara et al. [89] used feature threshold decision and Multivariate Statistical Process Control, respectively.

Billeci et al. [70] did not report results in terms of corrected FPR/h, as was done in this study. Additionally, none of the other studies specify how FPR/h was calculated. Thus, comparisons of FPR/h with these studies may not be valid.

The only research study specifying the SPH is Behbahani et al. [38], which tested several different values. However, the intervals used (between 1-3.5 min) were shorter than the one used in the present study. This may explain the high performance values obtained by Behbahani et al. [38], since shorter SPH intervals allow to capture changes in the signal which occur closer to the seizure onset and are probably more pronounced. Behbahani et al. [38] was also the only study to report the SOP, having tested several intervals between 1-8 min. Since our study employed a seizure-specific approach in the determination of the preictal intervals of the training seizures, there is high variability of SOP values, which range between 13 and 120 minutes. Thus, SOP values will not be discussed herein. However, we should consider that longer SOPs are undesirable from the viewpoint of the patient because they are translated into longer waiting times and thus result in increased anxiety.

Additionally, Behbahani et al. [38] was also the only study that performed statistical validation, even though not by comparison to the seizure-times surrogate, but instead to a random predictor (see Section 2.2.7). Lastly, the number of TLE

patients in the mentioned studies was relatively small, which may raise questions as to the statistical confidence in the results.

5.6.2 Comparative Analysis with Electroencephalogram (EEG) Studies

In this section, our results are compared with state-of-the-art EEG-based seizure prediction models. Table 5.7 shows the main characteristics and results of the present study and a selection of EEG seizure prediction studies including data from TLE patients in their analysis.

Table 5.7: Results obtained in the present study and state-of-the-art EEG-based studies.

Study	No. TLE Patients	Sensitivity (%)	FPR/h	Patients Validated (%)
Alvarado-Rojas et al. 2014 [98]	39	66	0.33	10
Teixeira et al. 2014 [99]	190	75.05	0.32	N.A.
Direito et al. 2017 [96]	130	38.13	0.23	N.A.
Pinto et al. 2021 [48]	19	38; 36; 37	1.03; 0.76; 0.58	32
This study (ANOVA F-test, Standard approach)	41	36.91	1.17	41.5
This study (ANOVA F-test, Hybrid approach)	41	36.26	0.72	41.5
This study (Kruskal-Wallis H-test, Standard approach)	41	30.12	1.06	36.6
This study (Kruskal-Wallis H-test, Hybrid approach)	41	32.64	0.97	36.6
This study (AUC, Standard approach)	41	30.69	1.51	39.0
This study (AUC, Hybrid approach)	41	29.76	0.87	39.0
This study (Feature-target correlation, Standard approach)	41	34.43	1.47	43.9
This study (Feature-target correlation, Hybrid approach)	41	25.24	0.42	36.6

After optimization of the SOP, Alvarado-Rojas et al. [98] reported a sensitivity of 66% and FPR/h of 0.33 h^{-1} for TLE patients. This performance largely surpasses that obtained with any of the approaches presented in the present study. Additionally, a percentage of 10% of validated patients was reported by comparison to a random predictor.

Teixeira et al. [99] also report increased performance, with a sensitivity of 75.05% and FPR/h of 0.32 h^{-1} for TLE patients. However, no statistical validation was performed to ensure that the algorithms performed above chance.

In a study with a total of 216 patients with various types of syndromes, Direito et al. 2017 [96] reported a sensitivity of 38.13% and a FPR/h of 0.23 h^{-1} for TLE patients. Although the authors achieved lower FPR/h, the sensitivity is only slightly higher than some of the values reported in this study. Additionally, even though the authors carried out statistical validation by comparison to a random predictor, they did not specify the percentage of TLE patients validated, mentioning only that 11% of the total dataset was validated.

Pinto et al. [48] developed an evolutionary algorithm for seizure prediction, reporting average sensitivities of 38%, 36% and 37% and FPR/h of 1.03 h^{-1}, 0.76 h^{-1} and 0.58 h^{-1}, for minimum SOP durations of 40, 50 and 60 minutes, respectively. Overall, performance above chance was obtained for 32% of patients by comparison to the seizure-times surrogate predictor. Thus, the results reported are similar to those obtained in the present study.

Once again, apart from the considerable difference introduced by analysing either ECG or EEG, we highlight other aspects in methodology that might contribute to the observed variability in the performance of our models and state-of-the-art models. Teixeira et al. [99] and Direito et al. [96] used SVM classifiers, although the former also used Artificial Neural Networks. Alvarado-Rojas et al. [98] used a threshold-based classifier, and Pinto et al. [48] used a logistic-regression classifier. Direito et al. [96], Alvarado-Rojas et al. [98] and Pinto et al. [48] reported results in terms of corrected FPR/h, while Teixeira et al. [99] did not. Teixeira et al. [99] and Direito et al. [96] specified an SPH of 10 seconds, a value sixty times smaller than the one used in this study, which may explain the attainment of higher performance values, and is inadequate for warning systems. Pinto et al. [48] used a SPH of 10 minutes, the same duration used in our study. Additionally, only Pinto et al. [48] carried out statistical validation by comparison to the seizure-times surrogates.

Lastly, it should be highlighted that the results for EEG and ECG seizure prediction models might be influenced by different aspects that may dictate the observation of high variability. The main factor lies in the different characteristics of each signal. The ECG has a defined trace characterized by a distinctive occurrence of R-peaks that allow for a relatively robust HRV analysis. The EEG trace is considered a more complex signal, that results from a sum of electrical potentials from different locations in the brain and that can be easily affected by noise. Additionally, both signals can be affected by circadian rhythms and alterations in

medication. Furthermore, the ECG signal may also reflect changes unrelated to the epileptogenic process due to alterations in emotional and psychological states (e.g., stress, anxiety), physical activity, and cardiac co-morbidities [8, 10, 49]. This can lead to increased rates of false alarms.

It is natural that, since epilepsy is a neurological condition and the ECG does not measure cerebral information, this signal presents a lower predictive power than the EEG. However, the comfort and ease associated with the acquisition of the ECG signal without causing social stigma (see Section 1.2), would be greatly appreciated by patients with epilepsy. Furthermore, it is possible that the ECG signal displays higher predictive capabilities for patients with certain characteristics (e.g., seizure types, sleep states). This would allow the development of seizure prediction systems focusing on patients with specific characteristics.

5.7 Patient Stratification

With the aim of assessing if the seizure prediction performance could be increased by restricting the dataset to subjects with certain characteristics, a patient stratification analysis was performed. The patients were selected based on the metadata contained in the EPILEPSIAE database (see Table 4.1) to form the following groups:

1. Patients with only FOA and/or FOIA seizures (11/41). This includes 24 FOA seizures and 34 FOIA seizures.
2. Patients who displayed only rhythmic activity patterns (20/41). This includes 114 seizures.
3. Patients who were awake during all seizures (17/41). This includes 96 seizures.
4. Male patients (24/41). This includes 135 seizures.
5. Female patients (17/41). This includes 103 seizures.

Table 5.8 shows the average and standard deviation values of the performance metrics obtained with each approach and feature selection method, as well as the proportion of validated patients. The performance obtained with the whole dataset is also included for easier comparison.

Upon analysis of the table, the group with only FOA and/or FOIA seizures always presents higher sensitivity when compared to the whole dataset, with differences that can exceed 20%. The percentage of validated patients also increases in most cases. However, we could see that, for this group of patients, when the sensitivity values increased, it typically led to an increase in FPR/h (as was always the case for the Hybrid approach).

Regarding the patients with only rhythmic activity patterns, there is no consistent pattern in the variation of sensitivity, FPR/h or percentage of validated patients. Thus, the performance improves in some cases but worsens in others.

Regarding the group of patients that only had seizures while awake, we observed no pattern for the sensitivity values when compared to the whole dataset. Conversely, FPR/h was found to consistently increase in the Standard approach and decrease in the Hybrid approach.

Concerning the group composed of male patients, it was also difficult to detect a specific pattern. In most of the cases, when using ANOVA F-test or Kruskal-Wallis H-test for feature selection, the sensitivity increases, while the opposite happens when using the other two feature selection methods. The same can be said about the proportion of validated patients. The FPR/h usually decreases in the Standard approach and increases in the Hybrid approach, when compared to the results obtained with the whole dataset. We were expecting that this group displayed an increase in performance, as per the discussion in Sections 2.5 and 3.1, where it was stated that male patients display higher rates of cardiovascular changes related to seizures. Lastly, regarding the group comprising only female patients, the opposite trend from that of the male patients is verified.

In summary, it is difficult to determine if the patient stratification allowed for an increase in performance in any of the groups analyzed. Although sensitivity increased when restricting the dataset to patients with only FOA and/or FOIA seizures, this was usually paired with an increase in FPR/h. Additionally, standard deviation values remained high in all groups, indicating high variability of results. This may motivate us to always perform patient stratification in order to analyze seizure prediction results separately for each group.

Table 5.8: Patient stratification results for each of the studies and feature selection methods.

Feature Selection Method	Approach	Stratification Group	Sensitivity (%)	FPR/h	Validated Patients
ANOVA F-test	Standard	**Whole Dataset**	**36.91±39.67**	**1.17±2.37**	**19/41 (46.3%)**
		FOA/FOIA	37.27±37.92	0.73±0.81	5/11 (45.5%)
		Rhythmic	34.67±40.90	0.87±1.09	8/20 (40.0%)
		Awake	30.10±40.27	1.19±2.91	7/17 (41.2%)
		Male	42.43±40.78	1.22±1.89	12/24 (50.0%)
		Female	29.12±36.67	1.09±2.91	7/17 (41.2%)
	Hybrid	**Whole Dataset**	**36.26±41.76**	**0.72±1.53**	**17/41 (41.5%)**
		FOA/FOIA	55.45±45.00	0.78±0.79	6/11 (54.5%)
		Rhythmic	38.83±44.94	0.66±1.10	8/20 (40.0%)
		Awake	40.29±46.41	0.59±0.68	8/17 (47.1%)
		Male	39.65±43.75	0.88±1.91	10/24 (41.7%)
		Female	31.47±38.26	0.51±0.65	7/17 (41.2%)
Kruskal-Wallis H-test	Standard	**Whole Dataset**	**30.12±37.77**	**1.06±2.17**	**14/41 (34.1%)**
		FOA/FOIA	33.18±40.02	0.78±1.04	3/11 (27.3%)
		Rhythmic	25.75±35.01	0.70±0.88	6/20 (30.0%)
		Awake	27.16±35.71	1.27±3.03	5/17 (29.4%)
		Male	35.00±39.00	0.90±1.22	9/24 (37.5%)
		Female	23.24±34.81	1.29±3.04	5/17 (29.4%)
	Hybrid	**Whole Dataset**	**32.64±37.94**	**0.97±1.67**	**15/41 (36.6%)**
		FOA/FOIA	49.09±37.04	1.67±2.42	5/11 (45.5%)
		Rhythmic	27.42±36.11	0.83±1.21	5/20 (25.0%)
		Awake	40.10±36.85	0.83±1.04	9/17 (52.9%)
		Male	31.18±36.96	1.10±1.99	8/24 (33.3%)
		Female	34.71±39.20	0.77±1.02	7/17 (41.2%)
AUC	Standard	**Whole Dataset**	**30.69±36.83**	**1.51±3.81**	**16/41 (39.0%)**
		FOA/FOIA	47.73±45.79	1.43±1.54	6/11 (54.5%)
		Rhythmic	36.67±38.22	1.10±1.92	9/20 (45.0%)
		Awake	29.41±42.21	1.94±5.43	6/17 (35.3%)
		Male	23.26±33.07	1.05±1.81	7/24 (29.2%)
		Female	41.18±39.24	2.16±5.45	9/17 (52.9%)
	Hybrid	**Whole Dataset**	**29.76±39.02**	**0.87±2.10**	**16/41 (39.0%)**
		FOA/FOIA	40.91±46.80	1.20±1.63	5/11 (45.5%)
		Rhythmic	39.17±42.25	0.90±1.65	9/20 (45.0%)
		Awake	29.61±39.77	0.61±1.34	7/17 (41.2%)
		Male	29.17±39.75	0.91±1.55	8/24 (33.3%)
		Female	30.59±37.96	0.81±2.70	8/17 (47.1%)
Feature-target Correlation	Standard	**Whole Dataset**	**34.43±38.89**	**1.47±4.43**	**19/41 (46.3%)**
		FOA/FOIA	57.73±45.30	3.15±7.66	7/11 (63.6%)
		Rhythmic	45.08±41.14	2.10±5.85	12/20 (60.0%)
		Awake	40.29±43.13	2.89±6.58	8/17 (47.1%)
		Male	33.75±43.31	0.67±0.94	9/24 (37.5%)
		Female	35.39±31.58	2.59±6.62	10/17 (58.8%)
	Hybrid	**Whole Dataset**	**25.24±34.89**	**0.42±0.73**	**15/41 (36.6%)**
		FOA/FOIA	46.36±45.18	0.61±0.80	6/11 (54.5%)
		Rhythmic	34.25±36.28	0.62±0.93	10/20 (50.0%)
		Awake	32.84±40.87	0.46±0.72	7/17 (41.2%)
		Male	30.62±38.06	0.61±0.89	9/24 (37.5%)
		Female	17.65±28.13	0.15±0.24	6/17 (35.3%)

6

Conclusion

The inspection of the preictal interval has the potential to bring great advantages to the field of seizure prediction. Besides the potential to enhance performance by improving the annotation of the data used to train the classifier, exploring this interval also represents an important step towards deeper understanding of the mechanisms of seizure generation, which are not yet well understood and seem to vary from seizure to seizure even within the same patient.

The present study focused on the development of HRV-based seizure prediction models in order to establish whether the inclusion of preictal information obtained with unsupervised learning methodologies could improve seizure prediction performance. To that end, we developed patient-specific seizure prediction methodologies and compared the results obtained with the Standard and the Hybrid approaches for preictal determination. The Standard approach consists of a seizure-specific grid-search in a range of discrete preictal intervals. The Hybrid approach integrates the clustering preictal information for the seizures for which solutions were obtained by Leal et al. [22], coupled with the grid-search for the remaining seizures.

It was successfully determined that the inclusion of clustering preictal information may, in some cases, improve the prediction performance, namely by reducing the FPR/h. Decreasing FPR/h would represent an improvement in seizure prediction, allowing the patient to be more confident in the seizure detection system. Additionally, no significant differences were found regarding sensitivity. However, we consider both approaches to have performed unsatisfactorily. When using information from clustering, we obtained 36.26 ± 41.76 % sensitivity and 0.72 ± 1.53 h^{-1} FPR/h, and models performed above chance for 41.5 % of patients.

Thus, since our models did not increase both measures of seizure prediction performance, we cannot state that unsupervised methodologies are required for preictal inspection, comparing to conventional grid-search methodologies. This may be related to the lower predictive power of the ECG signal when compared to the EEG, which determines that improved preictal interval annotation is not neces-

sarily translated into better performance. Alternatively, the changes in HRV captured by clustering algorithms may not reflect epileptogenic processes, but instead have been influenced by other internal or external factors which interfere with the cardio-respiratory function, such as emotional state, physical activity and circadian rhythms.

The work described in this document and in Leal et al. [22] represents the first steps in a novel perspective towards preictal inspection for improvement of seizure prediction performance. Taking into account the potential effect that an accurate seizure prediction system could have on the quality of life of a DRE patient, there are several aspects to explore in order to obtain more reliable results. Future work related to this topic includes:

- Application of unsupervised learning methodologies for preictal inspection to ECG data acquired in a real-life setting. The preictal intervals obtained need to be validated by incorporating them into a seizure prediction methodology and comparing the results obtained with the Standard and Hybrid approaches.
- Application of the unsupervised learning methodologies for preictal inspection to EEG data, and posterior validation of the resulting preictal information by incorporating it into a seizure prediction methodology and comparing the performance obtained with the Standard and Hybrid approaches. This would allow to reach final conclusions regarding the potential of unsupervised learning methods for the determination of the preictal interval.

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Appendices

A

Supplementary Results

A.1 Training Phase

Table A.1: Training parameters and performance in Standard approach with ANOVA F-test feature selection.

Patient	No. Seizures	Preictals (min)	C	F_{rel}	F_{final} (average)	SS_{sample}	SP_{sample}	MM_{sample}
402	3	40, 60, 20	2^{-8}	10	7.81	0.63	0.57	1.01
8902	3	120, 120, 100	2^{-4}	20	10.00	0.68	0.90	1.14
11002	3	80, 40, 80	2^{8}	20	12.26	0.87	0.49	1.07
16202	3	40, 20, 20	2^{-20}	10	2.13	0.79	0.76	1.10
21902	3	60, 20, 40	2^{-8}	20	9.32	0.82	0.74	1.11
23902	3	20, 100, 120	2^{0}	20	13.00	0.52	0.80	1.03
26102	3	120, 120, 120	2^{-12}	10	7.00	0.00	1.00	1.00
30802	3	120, 80, 20	2^{-12}	20	10.06	0.34	0.89	1.02
32702	3	60, 100, 100	2^{-4}	10	4.00	0.66	0.72	1.10
45402	3	120, 80, 120	2^{-12}	20	9.13	0.31	0.94	1.06
46702	3	60, 40, 40	2^{-12}	20	8.00	0.85	0.60	1.12
50802	3	20, 20, 40	2^{0}	10	7.00	0.48	0.84	1.03
52302	3	80, 20, 80	2^{-20}	10	6.00	0.75	0.57	1.05
53402	3	100, 20, 80	2^{-16}	20	11.00	0.65	0.69	1.10
55202	3	60, 120, 80	2^{-12}	10	7.00	0.64	0.66	1.11
56402	3	20, 120, 120	2^{-8}	10	9.00	0.00	0.96	0.96
58602	3	40, 120, 100	2^{-16}	20	11.71	0.66	0.66	1.12
59102	3	100, 40, 120	2^{-20}	10	5.06	0.63	0.72	1.12
60002	3	40, 40, 60	2^{-20}	10	7.97	0.85	0.66	1.09
64702	3	40, 120, 20	2^{-20}	10	4.74	0.93	0.26	1.01
75202	3	20, 60, 80	2^{8}	10	4.10	0.64	0.61	1.02
80702	3	20, 80, 60	2^{-4}	10	4.97	0.91	0.39	1.05
81102	3	120, 120, 120	2^{8}	10	7.00	0.01	1.00	1.00
85202	3	120, 120, 20	2^{-2}	10	1.00	0.31	0.91	1.06
93402	3	100, 20, 80	2^{8}	20	14.00	0.64	0.73	1.07
93902	3	20, 40, 120	2^{-16}	10	4.00	0.62	0.76	1.07
94402	3	120, 20, 120	2^{-12}	10	7.00	0.00	0.99	0.99
95202	3	20, 20, 20	2^{-16}	10	2.94	0.80	0.77	1.15
96002	3	60, 120, 120	2^{-8}	10	6.00	0.00	0.98	0.98
98102	3	80, 120, 120	2^{-12}	10	4.65	0.07	0.99	1.00
98202	3	20, 120, 100	2^{-4}	10	7.00	0.65	0.62	1.06
101702	3	60, 120, 120	2^{0}	20	7.00	0.17	0.96	1.01
102202	3	20, 60, 20	2^{-16}	20	8.81	0.66	0.58	1.06
104602	3	100, 80, 120	2^{-16}	10	4.97	0.84	0.56	1.06
109502	3	80, 20, 20	2^{-20}	10	4.00	0.60	0.66	0.98
110602	3	120, 20, 80	2^{8}	20	8.77	0.66	0.70	1.10
112802	3	120, 60, 120	2^{-8}	10	5.00	0.01	1.00	1.00
113902	3	120, 20, 20	2^{-12}	20	10.00	0.76	0.71	1.09
114702	3	20, 120, 120	2^{-8}	10	7.03	0.30	0.82	1.00
114902	3	120, 20, 60	2^{4}	10	4.16	0.69	0.36	0.99
123902	3	80, 20, 120	2^{-8}	20	7.03	0.57	0.88	1.11
Avg						0.54	0.74	1.05

C: SVM cost; F_{rel}: number of features chosen in the feature selection relevance step; F_{final}: final number of features (after the relevance and redundancy assessment steps); SS_{sample}: sample sensitivity; SP_{sample}: sample specificity; MM_{sample}: sample performance metric.

Table A.2: Training parameters and performance in Hybrid approach with ANOVA F-test feature selection.

Patient	No. Seizures	Preictals (min)	C	F_{rel}	F_{final} (average)	SS_{sample}	SP_{sample}	MM_{sample}
402	3	40, 60, 20	2^{-8}	10	7.94	0.63	0.57	1.01
8902	3	114.0, 60, 80	2^{8}	10	5.68	0.68	0.88	1.15
11002	2	120, 20	2^{8}	20	8.00	0.50	0.65	1.02
16202	3	25.3, 74.4, 2.73	2^{-20}	10	3.00	0.76	0.71	1.08
21902	3	60, 25.2, 99.03	2^{-8}	10	7.65	0.69	0.75	1.04
23902	3	40, 80, 120	2^{4}	20	11.03	0.47	0.88	1.03
26102	3	120, 100, 13.38	2^{-8}	10	7.00	0.29	0.64	0.93
30802	3	120, 80, 20	2^{-12}	20	10.06	0.34	0.89	1.02
32702	2	100, 70.78	2^{-12}	10	2.00	0.73	0.77	1.09
45402	3	93.6, 25.42, 80	2^{-20}	10	4.03	0.37	0.57	0.88
46702	3	5.95, 56.23, 120	2^{-16}	10	2.00	0.55	0.66	1.06
50802	3	66.25, 91.2, 77.58	2^{-20}	20	14.87	0.52	0.60	0.82
52302	3	80, 20, 80	2^{-20}	10	6.00	0.75	0.57	1.04
53402	3	100, 20, 80	2^{-16}	20	11.00	0.65	0.69	1.10
55202	3	0.62, 120, 20	2^{-20}	20	12.10	0.82	0.66	1.15
56402	3	15.1, 120, 120	2^{-8}	10	8.29	0.00	0.97	0.97
58602	3	34.35, 59.48, 100	2^{-8}	20	8.94	0.51	0.60	0.92
59102	3	116.42, 80, 120	2^{-16}	10	5.00	0.67	0.69	1.11
60002	3	38.23, 40, 60	2^{4}	10	7.97	0.85	0.66	1.08
64702	3	100, 37.13, 120	2^{-20}	10	4.58	0.14	0.90	0.94
75202	3	20, 60, 80	2^{8}	10	4.48	0.64	0.62	1.03
80702	3	60, 19.42, 61.33	2^{-20}	10	2.13	0.83	0.50	1.04
81102	3	120, 41.82, 120	2^{-8}	20	12.00	0.00	0.93	0.93
85202	3	79.65, 120, 37.47	2^{-20}	20	8.00	0.60	0.39	0.94
93402	3	100, 20, 80	2^{0}	20	14.00	0.64	0.73	1.07
93902	3	25.13, 60, 56.57	2^{-12}	10	4.00	0.61	0.65	1.00
94402	3	120, 31.82, 120	2^{-8}	20	11.81	0.01	0.99	0.99
95202	3	19.97, 97.6, 80	2^{-8}	20	7.00	0.44	0.74	0.97
96002	3	72.6, 120, 120	2^{-8}	10	4.00	0.01	0.97	0.97
98102	3	36.52, 120, 120	2^{-12}	20	12.71	0.06	0.99	1.00
98202	3	20, 120, 100	2^{4}	10	7.00	0.65	0.62	1.06
101702	3	80, 108.5, 20	2^{0}	10	2.87	0.33	0.62	0.93
102202	2	20, 40	2^{-8}	10	6.71	0.71	0.48	1.01
104602	3	100, 80, 120	2^{-16}	10	5.10	0.84	0.56	1.06
109502	3	60, 20, 44.03	2^{-8}	20	9.19	0.60	0.60	0.89
110602	3	120, 92.8, 2.2	2^{-20}	10	2.00	0.73	0.74	1.09
112802	3	62.3, 120, 20	2^{4}	20	9.00	0.51	0.47	0.86
113902	3	120, 20, 20	2^{-12}	20	10.00	0.76	0.71	1.09
114702	3	40.62, 20.15, 120	2^{-8}	10	5.00	0.33	0.67	1.00
114902	3	100, 20, 40	2^{8}	10	4.00	0.70	0.36	0.99
123902	3	120, 120, 0.4	2^{-8}	20	9.00	0.05	0.99	0.99
Avg						0.51	0.70	1.01

C: SVM cost; F_{rel}: number of features chosen in the feature selection relevance step; F_{final}: final number of features (after the relevance and redundancy assessment steps); SS_{sample}: sample sensitivity; SP_{sample}: sample specificity; MM_{sample}: sample performance metric.

Table A.3: Training parameters and performance in Standard approach with Kruskal-Wallis H-test feature selection.

Patient	No. Seizures	Preictals (min)	C	F_{rel}	F_{final} (average)	SS_{sample}	SP_{sample}	MM_{sample}
402	3	60, 20, 20	2^{-12}	10	10.00	0.65	0.47	1.01
8902	3	120, 60, 80	2^{0}	20	13.52	0.64	0.91	1.14
11002	3	20, 40, 80	2^{-20}	10	5.58	0.59	0.61	1.04
16202	3	20, 20, 20	2^{-20}	10	1.00	0.80	0.73	1.09
21902	3	60, 20, 40	2^{-4}	20	8.97	0.82	0.75	1.12
23902	3	20, 40, 20	2^{4}	20	9.71	0.62	0.84	1.06
26102	3	120, 120, 120	2^{-12}	10	7.00	0.00	1.00	1.00
30802	3	120, 60, 120	2^{-8}	20	7.00	0.25	0.92	1.02
32702	3	60, 100, 100	2^{-8}	10	4.00	0.65	0.75	1.10
45402	3	120, 80, 120	2^{-12}	20	9.16	0.28	0.96	1.06
46702	3	40, 40, 20	2^{4}	10	3.48	0.89	0.57	1.14
50802	3	60, 20, 80	2^{8}	20	10.00	0.59	0.75	1.05
52302	3	60, 40, 20	2^{-20}	10	5.00	0.64	0.56	1.05
53402	3	100, 20, 120	2^{-12}	10	5.68	0.58	0.74	1.08
55202	3	60, 120, 80	2^{-12}	10	7.00	0.64	0.66	1.11
56402	3	20, 120, 120	2^{-12}	10	9.90	0.00	0.98	0.98
58602	3	40, 120, 100	2^{-16}	20	9.65	0.66	0.67	1.13
59102	3	60, 100, 60	2^{-20}	10	5.71	0.74	0.68	1.12
60002	3	20, 40, 60	2^{-4}	20	12.19	0.82	0.76	1.12
64702	3	60, 120, 20	2^{-20}	20	10.00	0.93	0.23	1.00
75202	3	20, 60, 60	2^{-12}	20	10.00	0.71	0.64	1.04
80702	3	60, 20, 80	2^{0}	10	4.00	0.94	0.40	1.06
81102	3	120, 120, 120	2^{-8}	10	5.00	0.00	1.00	1.00
85202	3	120, 120, 20	2^{-12}	10	3.00	0.29	0.98	1.09
93402	3	120, 120, 20	2^{-12}	10	3.00	0.29	0.94	1.06
93902	3	20, 60, 120	2^{-8}	10	3.00	0.51	0.86	1.07
94402	3	120, 20, 120	2^{-8}	10	5.00	0.00	0.98	0.98
95202	3	20, 20, 20	2^{-12}	20	6.90	0.80	0.75	1.14
96002	3	60, 120, 120	2^{-8}	10	4.45	0.01	0.99	0.99
98102	3	80, 120, 120	2^{-12}	10	4.81	0.07	0.99	1.00
98202	3	20, 120, 100	2^{-4}	10	3.00	0.61	0.60	1.03
101702	3	20, 120, 120	2^{4}	20	11.00	0.20	0.95	1.01
102202	3	20, 40, 20	2^{-8}	10	5.16	0.65	0.58	1.06
104602	3	120, 100, 20	2^{8}	10	2.71	0.71	0.77	1.11
109502	3	100, 20, 20	2^{-20}	10	4.00	0.60	0.65	0.96
110602	3	120, 20, 80	2^{8}	20	8.77	0.66	0.69	1.09
112802	3	120, 100, 120	2^{-8}	20	10.74	0.00	1.00	1.00
113902	3	120, 20, 20	2^{-16}	10	6.00	0.79	0.71	1.11
114702	3	20, 120, 120	2^{-8}	10	7.71	0.29	0.84	1.00
114902	3	20, 20, 80	2^{-20}	10	6.00	0.56	0.59	0.96
123902	3	100, 40, 120	2^{-4}	20	7.45	0.60	0.87	1.08
Avg						0.51	0.76	1.05

C: SVM cost; F_{rel}: number of features chosen in the feature selection relevance step; F_{final}: final number of features (after the relevance and redundancy assessment steps); SS_{sample}: sample sensitivity; SP_{sample}: sample specificity; MM_{sample}: sample performance metric.

Table A.4: Training parameters and performance in Hybrid approach with Kruskal-Wallis H-test feature selection.

Patient	No. Seizures	Preictals (min)	C	F_{rel}	F_{final} (average)	SS_{sample}	SP_{sample}	MM_{sample}
402	3	40, 20, 20	2^{-12}	10	10.00	0.65	0.48	1.01
8902	3	114.0, 120, 100	2^{0}	20	10.84	0.61	0.90	1.12
11002	2	80, 120	2^{-8}	10	4.00	0.62	0.50	1.01
16202	3	25.3, 74.4, 2.73	2^{-16}	10	4.39	0.77	0.68	1.07
21902	3	60, 25.2, 99.03	2^{-8}	10	8.00	0.72	0.75	1.06
23902	3	20, 40, 20	2^{4}	20	9.81	0.64	0.84	1.06
26102	3	120, 120, 13.38	2^{-12}	10	2.00	0.00	0.95	0.95
30802	3	120, 60, 120	2^{-8}	20	7.00	0.25	0.92	1.02
32702	2	100, 70.78	2^{-16}	20	8.00	0.74	0.73	1.07
45402	3	93.6, 25.42, 100	2^{-20}	10	5.10	0.37	0.59	0.90
46702	3	5.95, 56.23, 100	2^{-20}	10	2.00	0.64	0.57	1.06
50802	3	66.25, 91.2, 77.58	2^{-20}	20	10.87	0.51	0.62	0.84
52302	3	60, 40, 20	2^{-20}	20	9.03	0.66	0.53	1.05
53402	3	20, 20, 60	2^{-16}	10	6.94	0.62	0.75	1.08
55202	3	0.62, 120, 20	2^{-16}	10	5.10	0.86	0.67	1.18
56402	3	15.1, 120, 120	2^{-8}	10	6.00	0.00	1.00	1.00
58602	3	34.35, 59.48, 100	2^{-20}	10	3.03	0.55	0.58	0.97
59102	3	116.42, 40, 120	2^{-16}	10	6.74	0.66	0.69	1.11
60002	3	38.23, 40, 40	2^{8}	10	6.00	0.85	0.67	1.09
64702	3	100, 37.13, 120	2^{8}	10	4.74	0.30	0.69	0.97
75202	3	20, 60, 60	2^{-12}	20	10.00	0.71	0.64	1.04
80702	3	60, 19.42, 61.33	2^{8}	10	2.94	0.83	0.46	1.04
81102	3	120, 41.82, 120	2^{-8}	10	8.55	0.00	0.98	0.98
85202	3	79.65, 120, 37.47	2^{-20}	20	8.00	0.59	0.42	0.94
93402	3	120, 120, 20	2^{-12}	10	3.00	0.29	0.94	1.06
93902	3	35.13, 60, 66.57	2^{-20}	10	3.00	0.62	0.69	1.01
94402	3	120, 31.82, 120	2^{-12}	20	8.77	0.00	0.98	0.98
95202	3	19.97, 97.6, 80	2^{-8}	20	7.00	0.42	0.75	0.99
96002	3	72.6, 120, 120	2^{-8}	10	3.00	0.01	0.98	0.98
98102	3	36.52, 120, 120	2^{-12}	20	11.84	0.04	0.99	1.00
98202	3	20, 120, 100	2^{-4}	10	3.03	0.61	0.60	1.02
101702	3	100, 108.5, 20	2^{-8}	10	2.00	0.34	0.60	0.93
102202	2	20, 80	2^{4}	10	4.00	0.54	0.52	1.00
104602	3	120, 100, 20	2^{8}	10	2.65	0.70	0.76	1.10
109502	3	40, 20, 44.03	2^{8}	20	9.13	0.53	0.61	0.90
110602	3	120, 92.8, 2.2	2^{-20}	10	3.00	0.63	0.72	1.06
112802	3	62.3, 60, 20	2^{4}	20	7.52	0.45	0.51	0.87
113902	3	120, 20, 20	2^{-16}	10	6.00	0.79	0.71	1.11
114702	3	40.62, 20.15, 120	2^{4}	10	5.13	0.33	0.67	1.00
114902	3	20, 20, 80	2^{-20}	10	6.00	0.57	0.59	0.97
123902	3	80, 40, 0.4	2^{-8}	10	3.00	0.82	0.61	1.03
Avg						0.51	0.70	1.02

C: SVM cost; F_{rel}: number of features chosen in the feature selection relevance step; F_{final}: final number of features (after the relevance and redundancy assessment steps); SS_{sample}: sample sensitivity; SP_{sample}: sample specificity; MM_{sample}: sample performance metric.

Table A.5: Training parameters and performance in Standard approach with AUC feature selection.

Patient	No. Seizures	Preictals (min)	C	F_{rel}	F_{final} (average)	SS_{sample}	SP_{sample}	MM_{sample}
402	3	120, 120, 120	2^{-16}	10	10.00	0.00	1.00	1.00
8902	3	80, 40, 60	2^{-20}	20	16.00	0.72	0.72	1.02
11002	3	120, 40, 80	2^{-4}	20	14.00	0.56	0.65	1.03
16202	3	20, 20, 20	2^{-16}	10	8.00	0.80	0.73	1.09
21902	3	60, 20, 100	2^{-12}	10	10.00	0.70	0.74	1.02
23902	3	20, 20, 20	2^{-4}	10	10.00	0.49	0.90	1.07
26102	3	120, 120, 120	2^{-8}	20	15.00	0.00	1.00	1.00
30802	3	120, 100, 20	2^{-12}	20	14.00	0.36	0.86	1.02
32702	3	20, 100, 120	2^{-12}	20	15.00	0.31	0.89	1.04
45402	3	120, 120, 120	2^{-16}	20	12.00	0.35	0.92	1.02
46702	3	60, 60, 40	2^{8}	20	12.00	0.88	0.59	1.13
50802	3	20, 120, 40	2^{-20}	20	12.00	0.59	0.78	1.02
52302	3	20, 40, 20	2^{-12}	20	14.00	0.72	0.59	1.00
53402	3	20, 40, 60	2^{-16}	20	12.00	0.67	0.69	1.07
55202	3	40, 120, 80	2^{-20}	20	13.45	0.60	0.65	1.03
56402	3	20, 120, 120	2^{-8}	10	9.00	0.00	0.99	0.99
58602	3	20, 120, 100	2^{4}	10	10.00	0.61	0.85	1.12
59102	3	20, 80, 100	2^{-16}	20	16.00	0.75	0.70	1.07
60002	3	20, 40, 20	2^{-4}	20	15.00	0.91	0.83	1.24
64702	3	20, 80, 20	2^{-8}	10	9.00	0.65	0.55	1.01
75202	3	120, 120, 20	2^{-12}	20	15.00	0.01	1.00	1.00
80702	3	60, 20, 60	2^{-4}	10	10.00	0.78	0.66	1.06
81102	3	120, 120, 40	2^{-12}	10	10.00	0.12	1.00	1.01
85202	3	20, 120, 120	2^{-16}	10	10.00	0.00	1.00	1.00
93402	3	120, 120, 120	$2^{-12}4$	10	10.00	0.00	1.00	1.00
93902	3	120, 60, 100	2^{-16}	20	14.00	0.64	0.78	1.02
94402	3	120, 40, 120	2^{8}	20	14.00	0.20	0.95	0.99
95202	3	20, 20, 20	2^{-8}	20	9.97	0.84	0.82	1.19
96002	3	20, 120, 120	2^{-12}	10	9.00	0.03	1.00	1.00
98102	3	20, 120, 120	2^{-12}	10	10.00	0.00	1.00	1.00
98202	3	120, 120, 120	2^{-12}	10	10.00	0.01	1.00	1.00
101702	3	20, 120, 120	2^{8}	20	14.00	0.26	0.92	1.02
102202	3	20, 40, 20	2^{-12}	20	13.00	0.62	0.59	1.04
104602	3	100, 80, 120	2^{-20}	20	10.39	0.83	0.53	1.04
109502	3	40, 20, 40	2^{4}	10	10.00	0.58	0.72	0.98
110602	3	120, 80, 80	2^{-12}	10	10.00	0.64	0.66	1.05
112802	3	120, 20, 120	2^{-8}	10	10.00	0.01	0.98	0.98
113902	3	40, 20, 100	2^{-8}	20	13.00	0.66	0.79	1.04
114702	3	20, 120, 120	2^{-16}	10	10.00	0.00	1.00	1.00
114902	3	40, 120, 120	2^{-12}	10	10.00	0.02	0.96	0.96
123902	3	60, 20, 120	2^{-4}	20	13.00	0.49	0.92	1.04
Avg						0.42	0.83	1.03

C: SVM cost; F_{rel}: number of features chosen in the feature selection relevance step; F_{final}: final number of features (after the relevance and redundancy assessment steps); SS_{sample}: sample sensitivity; SP_{sample}: sample specificity; MM_{sample}: sample performance metric.

Table A.6: Training parameters and performance in Hybrid approach with AUC feature selection.

Patient	No. Seizures	Preictals (min)	C	F_{rel}	F_{final} (average)	SS_{sample}	SP_{sample}	MM_{sample}
402	3	120, 120, 120	2^{-16}	10	10.00	0.00	1.00	1.00
8902	3	114.0, 20, 20	2^{-12}	10	10.00	0.24	0.94	1.03
11002	2	20, 20	2^{-20}	10	9.00	0.29	0.33	0.44
16202	3	25.3, 74.4, 2.73	2^{-16}	10	9.00	0.76	0.67	1.06
21902	3	60, 25.2, 99.03	2^{-8}	20	16.00	0.73	0.65	0.97
23902	3	20, 20, 20	2^{-4}	10	10.00	0.49	0.90	1.08
26102	3	120, 120, 13.38	2^{-12}	10	9.00	0.00	0.99	0.99
30802	3	120, 100, 20	2^{-12}	20	14.00	0.36	0.86	1.02
32702	2	100, 70.78	2^{-12}	20	16.00	0.70	0.71	1.04
45402	3	93.6, 25.42, 120	2^{-12}	10	10.00	0.32	0.63	0.85
46702	3	5.95, 56.23, 120	2^{-16}	10	10.00	0.50	0.69	1.03
50802	3	66.25, 91.2, 77.58	2^{-20}	10	10.00	0.57	0.57	0.82
52302	3	20, 20, 20	2^{-20}	10	9.00	0.61	0.64	0.90
53402	3	20, 40, 60	2^{-16}	20	12.00	0.67	0.70	1.07
55202	3	0.62, 120, 80	2^{-20}	20	13.00	0.69	0.68	1.06
56402	3	15.1, 20, 20	2^{-20}	10	8.23	0.51	0.67	0.89
58602	3	43.35, 59.48, 100	2^{-8}	10	10.00	0.56	0.62	0.94
59102	3	116.42, 20, 40	2^{-20}	20	15.00	0.66	0.60	1.00
60002	3	38.23, 40, 20	2^{-8}	10	9.00	0.79	0.74	1.09
64702	3	20, 37.13, 40	2^{8}	10	9.00	0.57	0.61	0.95
75202	3	120, 120, 20	2^{-12}	20	15.00	0.01	1.00	1.00
80702	3	60, 19.42, 61.33	2^{-8}	10	10.00	0.81	0.63	1.07
81102	3	120, 41.82, 120	2^{-12}	10	10.00	0.01	0.95	0.95
85202	3	79.65, 120, 37.47	2^{-12}	10	10.00	0.18	0.76	0.78
93402	3	120, 120, 120	2^{-12}	10	10.00	0.00	1.00	1.00
93902	3	25.13, 60, 56.57	2^{-20}	10	9.00	0.67	0.67	0.97
94402	3	120, 31.82, 120	2^{8}	20	14.00	0.20	0.95	0.99
95202	3	19.97, 97.6, 120	2^{-16}	10	10.00	0.28	0.77	0.96
96002	3	72.6, 120, 120	2^{-8}	20	11.00	0.00	0.99	0.99
98102	3	36.52, 120, 120	2^{-12}	20	12.00	0.00	1.00	1.00
98202	3	120, 120, 120	2^{-12}	10	10.00	0.01	1.00	1.00
101702	3	100, 108.5, 20	2^{-12}	10	9.00	0.40	0.60	0.91
102202	2	20, 120	2^{-8}	20	10.00	0.50	0.53	1.00
104602	3	100, 80, 120	2^{-20}	20	10.29	0.83	0.53	1.04
109502	3	40, 40, 44.03	2^{8}	20	9.74	0.58	0.68	0.96
110602	3	100, 92.8, 2.2	2^{0}	20	16.00	0.59	0.84	1.05
112802	3	62.3, 100, 20	2^{0}	10	10.00	0.51	0.53	0.80
113902	3	40, 20, 100	2^{-8}	20	13.00	0.66	0.79	1.04
114702	3	40.62, 20.15, 120	2^{-12}	20	12.00	0.26	0.69	0.93
114902	3	40, 120, 120	2^{-12}	10	10.00	0.02	0.96	0.96
123902	3	120, 120, 0.4	2^{-16}	20	10.00	0.05	1.00	1.00
Avg						0.40	0.76	0.97

C: SVM cost; F_{rel}: number of features chosen in the feature selection relevance step; F_{final}: final number of features (after the relevance and redundancy assessment steps); SS_{sample}: sample sensitivity; SP_{sample}: sample specificity; MM_{sample}: sample performance metric.

Table A.7: Training parameters and performance in Standard approach with feature-target correlation feature selection.

Patient	No. Seizures	Preictals (min)	C	F_{rel}	F_{final} (average)	SS_{sample}	SP_{sample}	MM_{sample}
402	3	120, 120, 120	2^{-16}	10	10.00	0.00	1.00	1.00
8902	3	120, 20, 20	2^{-12}	10	10.00	0.25	0.93	1.02
11002	3	120, 40, 80	2^{0}	20	13.00	0.58	0.66	1.04
16202	3	40, 20, 20	2^{-12}	10	8.00	0.80	0.74	1.10
21902	3	120, 120, 120	2^{-12}	20	13.00	0.01	1.00	1.00
23902	3	20, 20, 40	2^{-8}	10	10.00	0.51	0.88	1.08
26102	3	120, 120, 120	2^{-8}	20	13.00	0.00	1.00	1.00
30802	3	120, 100, 20	2^{-12}	20	13.32	0.35	0.87	1.02
32702	3	20, 100, 120	2^{-8}	20	14.00	0.30	0.91	1.05
45402	3	20, 20, 20	2^{-16}	10	10.00	0.48	0.56	0.77
46702	3	60, 20, 40	2^{-12}	20	13.00	0.89	0.55	1.11
50802	3	20, 120, 40	2^{-20}	20	11.00	0.60	0.77	1.01
52302	3	120, 20, 120	2^{-12}	20	11.00	0.00	1.00	1.00
53402	3	120, 20, 40	2^{-12}	20	12.58	0.44	0.91	1.06
55202	3	20, 120, 80	2^{-20}	20	11.00	0.58	0.66	1.04
56402	3	20, 120, 120	$2^{-8}3$	10	9.00	0.00	0.99	0.99
58602	3	20, 120, 100	2^{-12}	20	14.00	0.56	0.85	1.10
59102	3	60, 80, 100	2^{8}	20	14.00	0.58	0.78	1.01
60002	3	120, 60, 20	2^{8}	20	14.00	0.31	0.96	1.07
64702	3	20, 120, 120	2^{-12}	20	15.00	0.00	1.00	1.00
75202	3	120, 120, 20	2^{-8}	20	14.00	0.01	1.00	1.00
80702	3	60, 20, 60	2^{-8}	20	13.00	0.83	0.61	1.06
81102	3	120, 120, 20	2^{-8}	10	10.00	0.00	1.00	1.00
85202	3	20, 120, 120	2^{-16}	10	10.00	0.00	1.00	1.00
93402	3	20, 20, 20	2^{-20}	10	10.00	0.14	0.35	0.40
93902	3	120, 60, 100	2^{-16}	20	12.00	0.65	0.78	1.02
94402	3	120, 20, 120	2^{-8}	20	15.00	0.01	0.99	0.99
95202	3	20, 20, 20	2^{-8}	20	11.00	0.84	0.81	1.18
96002	3	20, 20, 20	2^{-8}	10	9.00	0.45	0.59	0.76
98102	3	120, 120, 120	2^{-12}	20	13.00	0.04	1.00	1.00
98202	3	20, 80, 100	2^{-16}	10	10.00	0.74	0.68	1.01
101702	3	20, 120, 120	2^{-12}	10	9.00	0.00	1.00	1.00
102202	3	20, 40, 20	2^{-12}	20	12.00	0.66	0.55	1.04
104602	3	100, 100, 120	2^{-16}	20	9.00	0.77	0.59	1.01
109502	3	40, 120, 100	2^{-12}	10	10.00	0.30	0.78	0.95
110602	3	80, 100, 20	2^{0}	20	16.00	0.71	0.83	1.10
112802	3	120, 20, 120	2^{-8}	10	10.00	0.01	0.99	0.99
113902	3	40, 20, 100	2^{-12}	20	13.00	0.70	0.75	1.03
114702	3	20, 20, 20	2^{-16}	10	9.00	0.39	0.52	0.68
114902	3	120, 20, 120	2^{-20}	10	9.00	0.31	0.75	0.99
123902	3	80, 20, 120	2^{-4}	20	12.00	0.55	0.90	1.06
Avg						0.37	0.82	0.99

C: SVM cost; F_{rel}: number of features chosen in the feature selection relevance step; F_{final}: final number of features (after the relevance and redundancy assessment steps); SS_{sample}: sample sensitivity; SP_{sample}: sample specificity; MM_{sample}: sample performance metric.

Table A.8: Training parameters and performance in Hybrid approach with feature-target correlation feature selection.

Patient	No. Seizures	Preictals (min)	C	F_{rel}	F_{final} (average)	SS_{sample}	SP_{sample}	MM_{sample}
402	3	120, 120, 120	2^{-16}	10	10.00	0.00	1.00	1.00
8902	3	114.0, 20, 20	2^{-12}	10	10.00	0.26	0.95	1.05
11002	2	20, 20	2^{-16}	10	7.61	0.18	0.39	0.45
16202	3	25.3, 74.4, 2.73	2^{-16}	10	9.00	0.76	0.67	1.06
21902	3	20, 25.2, 99.03	2^{8}	20	11.45	0.60	0.68	0.91
23902	3	20, 20, 40	2^{-8}	10	10.00	0.51	0.88	1.08
26102	3	120, 120, 13.38	2^{-20}	10	9.00	0.00	0.99	0.99
30802	3	120, 100, 20	2^{-12}	20	13.29	0.35	0.87	1.02
32702	2	100, 70.78	2^{-12}	20	15.00	0.70	0.71	1.04
45402	3	93.6, 25.42, 120	2^{-12}	10	10.00	0.30	0.74	0.96
46702	3	5.95, 56.23, 20	2^{-16}	20	12.00	0.48	0.67	1.02
50802	3	66.25, 91.2, 77.58	2^{-20}	10	10.00	0.61	0.60	0.86
52302	3	120, 20, 120	2^{-12}	20	11.00	0.00	1.00	1.00
53402	3	120, 20, 40	2^{-12}	20	12.55	0.44	0.91	1.06
55202	3	0.62, 120, 80	2^{-16}	20	11.00	0.68	0.69	1.06
56402	3	15.1, 120, 120	2^{-8}	10	9.00	0.00	0.99	0.99
58602	3	34.35, 59.48, 80	2^{-4}	20	12.00	0.60	0.54	0.97
59102	3	116.42, 40, 100	2^{4}	20	14.00	0.50	0.67	0.93
60002	3	38.23, 40, 20	2^{-8}	10	9.00	0.57	0.77	1.01
64702	3	120, 37.13, 120	2^{-8}	20	16.00	0.24	0.78	0.93
75202	3	120, 120, 20	2^{-8}	20	14.00	0.01	1.00	1.00
80702	3	60, 19.42, 61.33	2^{-8}	10	10.00	0.85	0.62	1.07
81102	3	120, 41.82, 120	2^{-12}	10	10.00	0.01	0.96	0.96
85202	3	79.65, 120, 37.47	2^{-8}	10	10.00	0.15	0.75	0.76
93402	3	20, 20, 20	2^{-12}	10	10.00	0.11	0.37	0.39
93902	3	25.13, 60, 56.57	2^{-12}	10	9.00	0.66	0.67	0.99
94402	3	120, 31.82, 120	2^{8}	20	15.00	0.11	0.97	0.99
95202	3	19.97, 97.6, 20	2^{-20}	10	7.00	0.78	0.65	1.06
96002	3	72.6, 20, 20	2^{0}	10	9.00	0.49	0.66	0.82
98102	3	36.52, 120, 120	2^{-2}	20	13.00	0.00	1.00	1.00
98202	3	20, 80, 100	2^{-16}	10	10.00	0.74	0.68	1.01
101702	3	80, 108.5, 20	2^{-16}	20	13.84	0.45	0.57	0.89
102202	2	20, 120	2^{-8}	20	8.45	0.50	0.53	1.00
104602	3	100, 100, 120	2^{-16}	20	9.00	0.77	0.59	1.01
109502	3	40, 120, 44.03	2^{4}	10	10.00	0.26	0.79	0.90
110602	3	80, 92.8, 2.2	2^{4}	20	16.00	0.71	0.83	1.10
112802	3	62.3, 40, 20	2^{-20}	10	10.00	0.50	0.58	0.85
113902	3	40, 20, 100	2^{-12}	20	13.00	0.70	0.75	1.03
114702	3	40.62, 20.15, 120	2^{-12}	20	10.03	0.27	0.69	0.94
114902	3	120, 20, 120	2^{-20}	10	9.00	0.31	0.74	0.99
123902	3	20, 20, 0.4	2^{0}	10	8.00	0.16	0.81	0.83
Avg						0.40	0.75	0.95

C: SVM cost; F_{rel}: number of features chosen in the feature selection relevance step; F_{final}: final number of features (after the relevance and redundancy assessment steps); SS_{sample}: sample sensitivity; SP_{sample}: sample specificity; MM_{sample}: sample performance metric.

A.2 Testing Phase

Table A.9: Testing parameters and performance in the Standard approach with ANOVA F-test feature selection.

Patient	No. Test Seizures	Preictal (min)	T	SS_{method} (%)	FPR/h	SS_{surr} (%)	P-value	Above Chance
402	1	40.00	0.60	0.00	1.66	50.00±50.00	-	No
8902	2	113.33	0.15	100.00	0.67	10.00±20.00	4.256×10^{-21}	Yes
11002	2	66.67	0.45	50.00	1.11	50.00±38.73	-	No
16202	4	26.67	0.25	75.00	12.59	65.00±27.84	3.144×10^{-2}	Yes
21902	1	40.00	0.30	0.00	0.00	0.00±0.00	-	No
23902	2	80.00	0.20	50.00	0.76	50.00±34.16	-	No
26102	1	120.00	0.10	0.00	0.00	0.00±0.00	-	No
30802	5	73.33	0.25	60.00	0.58	30.00±16.93	9.459×10^{-11}	Yes
32702	2	86.67	0.40	100.00	0.64	30.00±24.49	8.655×10^{-16}	Yes
45402	1	106.67	0.15	0.00	0.00	0.00±0.00	-	No
46702	2	46.67	0.30	50.00	0.89	40.00±20.00	5.827×10^{-3}	Yes
50802	2	26.67	0.25	0.00	0.81	23.33±28.09	-	No
52302	2	60.00	0.45	50.00	1.07	48.33±30.23	3.843×10^{-1}	No
53402	1	66.67	0.30	100.00	0.40	0.00±0.00	0.000	Yes
55202	5	86.67	0.65	20.00	0.00	0.00±0.00	0.000	Yes
56402	3	86.67	0.10	0.00	0.00	0.00±0.00	-	No
58602	4	86.67	0.25	50.00	2.74	69.17±22.99	-	No
59102	2	86.67	0.25	0.00	0.69	40.00±20.00	-	No
60002	3	46.67	0.30	100.00	3.72	54.44±26.50	1.850×10^{-10}	Yes
64702	2	60.00	0.85	0.00	0.00	0.00±0.00	-	No
75202	4	53.33	0.25	100.00	8.84	74.17±23.70	1.141×10^{-6}	Yes
80702	4	53.33	0.75	0.00	0.09	12.50±12.50	-	No
81102	2	120.00	0.10	0.00	0.00	0.00±0.00	-	No
85202	2	86.67	0.25	0.00	0.00	0.00±0.00	-	No
93402	2	66.67	0.40	100.00	0.53	33.33±23.57	1.131×10^{-15}	Yes
93902	3	60.00	0.25	66.67	3.41	73.33±23.41	-	No
94402	4	86.67	0.10	0.00	0.00	0.00±0.00	-	No
95202	4	20.00	0.20	25.00	0.33	11.67±14.04	9.269×10^{-6}	Yes
96002	4	100.00	0.10	0.00	0.00	0.00±0.00	-	No
98102	2	106.67	0.10	0.00	0.00	0.00±0.00	-	No
98202	4	80.00	0.10	100.00	0.76	44.17±21.10	6.248×10^{-15}	Yes
101702	2	100.00	0.10	50.00	0.37	36.67±22.11	1.470×10^{-3}	Yes
102202	4	33.33	0.40	25.00	0.49	16.67±11.79	3.361×10^{-4}	Yes
104602	2	100.00	0.45	0.00	0.00	0.00±0.00	-	No
109502	2	40.00	0.40	100.00	1.85	53.33±22.11	1.674×10^{-12}	Yes
110602	2	73.33	0.60	0.00	1.90	78.33±27.94	-	No
112802	3	100.00	0.10	66.67	0.46	40.00±20.00	3.324×10^{-8}	Yes
113902	4	53.33	0.50	0.00	0.00	0.00±0.00	-	No
114702	6	86.67	0.50	0.00	0.00	0.00±0.00	-	No
114902	4	66.67	0.75	75.00	0.55	40.83 ±15.12	3.199×10^{-13}	Yes
123902	2	73.33	0.10	0.00	0.00	0.00±0.00	-	No
Avg				36.91	1.17		**Total**	17

T: firing power threshold; SS_{method}: seizure prediction method sensitivity.; SS_{surr}: surrogate sensitivity; Avg: average.

Table A.10: Testing parameters and performance in the Hybrid approach with ANOVA F-test feature selection.

Patient	No. Test Seizures	Preictal (min)	T	SS_{method} (%)	FPR/h	SS_{surr} (%)	P-value	Above Chance
402	1	40.00	0.60	0.00	1.74	46.67±49.89	-	No
8902	2	84.67	0.15	100.00	0.68	28.33±35.78	5.783×10^{-12}	Yes
11002	2	70.00	0.65	0.00	0.00	0.00±0.00	-	No
16202	4	34.14	0.85	25.00	0.17	6.67±11.06	4.026×10^{-10}	Yes
21902	1	61.41	0.30	0.00	0.00	0.00±0.00	-	No
23902	2	80.00	0.10	100.00	1.72	53.33±36.36	6.773×10^{-8}	Yes
26102	1	77.79	0.80	0.00	0.00	0.00±0.00	-	No
30802	5	73.33	0.25	60.00	0.56	40.67±16.72	4.282×10^{-7}	Yes
32702	2	85.39	0.60	100.00	0.21	45.00±15.00	1.161×10^{-18}	Yes
45402	1	73.01	0.65	100.00	2.29	83.33±37.27	1.130×10^{-2}	Yes
46702	2	60.73	0.90	0.00	0.00	0.00±0.00	-	No
50802	2	78.34	0.55	50.00	0.00	0.00±0.00	0.000	Yes
52302	2	60.00	0.45	50.00	1.07	58.33±29.11	-	No
53402	1	66.67	0.30	100.00	0.40	0.00±0.00	0.000	Yes
55202	5	46.87	0.35	60.00	0.75	38.00±20.88	1.955×10^{-6}	Yes
56402	3	85.03	0.10	0.00	0.00	0.00±0.00	-	No
58602	3	64.61	0.65	0.00	0.29	25.56±14.10	-	No
59102	2	105.47	0.35	0.00	0.33	26.67±24.94	-	No
60002	3	46.08	0.30	66.67	4.42	65.56±25.07	4.065×10^{-1}	No
64702	2	85.71	0.25	0.00	0.00	0.00±0.00	-	No
75202	4	53.33	0.25	100.00	8.78	80.83±20.09	8.630×10^{-6}	Yes
80702	4	46.92	0.85	0.00	0.40	30.00±18.71	-	No
81102	2	93.94	0.20	0.00	0.00	0.00±0.00	-	No
85202	2	79.04	0.80	0.00	0.00	0.00±0.00	-	No
93402	2	66.67	0.40	100.00	0.65	31.67±24.09	1.055×10^{-15}	Yes
93902	3	47.23	0.60	0.00	0.00	0.00±0.00	-	No
94402	4	90.61	0.10	0.00	0.00	0.00±0.00	-	No
95202	4	65.86	0.40	50.00	0.73	28.33±15.46	1.270×10^{-8}	Yes
96002	4	104.20	0.10	0.00	0.00	0.00±0.00	-	No
98102	1	92.17	0.10	0.00	0.00	0.00±0.00	-	No
98202	4	80.00	0.10	100.00	0.76	45.00±17.56	7.847×10^{-17}	Yes
101702	2	69.50	0.30	50.00	2.03	50.00±31.62	-	No
102202	4	30.00	0.90	25.00	0.08	6.67±11.06	4.026×10^{-10}	Yes
104602	2	100.00	0.45	0.00	0.00	0.00±0.00	-	No
109502	1	41.34	0.45	100.00	0.00	0.00±0.00	0.000	Yes
110602	2	71.67	0.65	100.00	0.71	26.67±24.94	4.141×10^{-16}	Yes
112802	3	67.43	0.80	0.00	0.29	23.33±15.28	-	No
113902	4	53.33	0.50	0.00	0.00	0.00±0.00	-	No
114702	6	60.26	0.85	0.00	0.00	0.00±0.00	-	No
114902	4	53.33	0.90	50.00	0.60	33.33±16.24	2.951×10^{-6}	Yes
123902	2	80.13	0.10	0.00	0.00	0.00±0.00	-	No
Avg				36.26	0.72		**Total**	17

T: firing power threshold; SS_{method}: seizure prediction method sensitivity.; SS_{surr}: surrogate sensitivity; Avg: average.

Table A.11: Testing parameters and performance in the Standard approach with Kruskal-Wallis H-test feature selection.

Patient	No. Test Seizures	Preictal (min)	T	SS_{method} (%)	FPR/h	SS_{surr} (%)	P-value	Above Chance
402	1	33.33	0.75	0.00	1.40	43.33±49.55	-	No
8902	2	86.67	0.15	100.00	0.68	36.67±36.36	1.383×10^{-10}	Yes
11002	2	46.67	0.25	50.00	0.91	40.00±20.00	5.827×10^{-3}	Yes
16202	4	20.00	0.20	25.00	13.14	50.00±20.41	-	No
21902	1	40.00	0.30	0.00	0.00	0.00±0.00	-	No
23902	2	26.67	0.20	50.00	1.80	40.00±32.66	5.498×10^{-2}	No
26102	1	120.00	0.10	0.00	0.00	0.00±0.00	-	No
30802	5	100.00	0.25	40.00	0.00	0.00±0.00	0.000	Yes
32702	2	86.67	0.30	100.00	0.64	25.00±25.00	2.440×10^{-16}	Yes
45402	1	106.67	0.10	0.00	0.00	0.00±0.00	-	No
46702	2	33.33	0.35	0.00	1.38	36.67±22.11	-	No
50802	2	53.33	0.40	50.00	0.00	0.00±0.00	0.000	Yes
52302	2	40.00	0.40	0.00	1.74	50.00±28.87	-	No
53402	1	80.00	0.15	100.00	0.00	0.00±0.00	0.000	Yes
55202	5	86.67	0.70	20.00	0.00	0.00±0.00	0.000	Yes
56402	3	86.67	0.10	0.00	0.00	0.00±0.00	-	No
58602	4	86.67	0.20	75.00	3.30	69.17±26.37	1.216×10^{-1}	No
59102	2	73.33	0.35	0.00	0.26	31.67±24.09	-	No
60002	3	40.00	0.25	33.33	1.89	46.67±25.24	-	No
64702	2	66.67	0.90	0.00	0.00	0.00±0.00	-	No
75202	4	46.67	0.40	100.00	4.57	65.83±24.57	1.481×10^{-8}	Yes
80702	4	53.33	0.70	25.00	0.20	10.83±15.39	1.427×10^{-5}	Yes
81102	2	120.00	0.10	0.00	0.00	0.00±0.00	-	No
85202	2	86.67	0.10	0.00	0.00	0.00±0.00	-	No
93402	2	86.67	0.15	0.00	0.00	0.00±0.00	-	No
93902	3	66.67	0.10	100.00	2.83	66.67±28.54	3.620×10^{-7}	Yes
94402	4	86.67	0.10	0.00	0.00	0.00±0.00	-	No
95202	4	20.00	0.15	50.00	0.78	14.17±15.39	1.544×10^{-13}	Yes
96002	4	100.00	0.10	0.00	0.00	0.00±0.00	-	No
98102	2	106.67	0.10	0.00	0.00	0.00±0.00	-	No
98202	4	80.00	0.20	75.00	1.04	44.17±22.99	2.972×10^{-8}	Yes
101702	2	86.67	0.10	0.00	0.68	36.67±22.11	-	No
102202	4	26.67	0.50	0.00	0.57	15.00±12.25	-	No
104602	2	80.00	0.10	0.00	0.00	0.00±0.00	-	No
109502	2	46.67	0.50	100.00	1.28	35.00±26.30	3.515×10^{-14}	Yes
110602	2	73.33	0.60	0.00	1.90	75.00±33.54	-	No
112802	3	113.33	0.10	66.67	0.53	30.00±21.69	2.652×10^{-10}	Yes
113902	4	53.33	0.55	0.00	0.00	0.00±0.00	-	No
114702	6	86.67	0.45	0.00	0.00	0.00±0.00	-	No
114902	4	40.00	0.10	75.00	2.05	51.67±15.72	4.093×10^{-9}	Yes
123902	2	86.67	0.15	0.00	0.00	0.00±0.00	-	No
Avg				30.12	1.06		**Total**	15

T: firing power threshold; SS_{method}: seizure prediction method sensitivity.; SS_{surr}: surrogate sensitivity; Avg: average.

Table A.12: Testing parameters and performance in the Hybrid approach with Kruskal-Wallis H-test feature selection.

Patient	No. Test Seizures	Preictal (min)	T	SS_{method} (%)	FPR/h	SS_{surr} (%)	P-value	Above Chance
402	1	26.67	0.70	0.00	3.17	43.33±49.55	-	No
8902	2	111.33	0.15	100.00	0.68	20.00 ±27.69	6.510×10^{-16}	Yes
11002	2	100.00	0.80	0.00	0.00	0.00±0.00	-	No
16202	4	34.14	0.90	25.00	0.00	0.00±0.00	0.000	Yes
21902	1	61.41	0.30	0.00	0.00	0.00±0.00	-	No
23902	2	26.67	0.20	50.00	2.57	45.00±32.53	2.073×10^{-1}	No
26102	1	84.46	0.15	0.00	0.00	0.00±0.00	-	No
30802	5	100.00	0.25	40.00	0.00	0.00±0.00	0.000	Yes
32702	2	85.39	0.60	100.00	0.21	41.67±18.63	7.962×10^{-17}	Yes
45402	1	73.01	0.50	100.00	2.89	93.33±24.94	8.039×10^{-2}	No
46702	2	54.06	0.75	0.00	0.49	43.33±17.00	-	No
50802	2	78.34	0.65	0.00	0.00	0.00±0.00	-	No
52302	2	40.00	0.45	50.00	1.32	45.00±29.86	1.873×10^{-1}	No
53402	1	33.33	0.25	100.00	8.67	70.00±45.83	7.129×10^{-4}	Yes
55202	5	46.87	0.40	40.00	0.67	30.67±20.48	1.019×10^{-2}	Yes
56402	3	85.03	0.10	0.00	0.00	0.00±0.00	-	No
58602	3	64.61	0.50	0.00	0.86	47.78±22.25	-	No
59102	2	92.14	0.35	50.00	0.31	28.33±24.78	2.845×10^{-5}	Yes
60002	3	39.41	0.35	66.67	3.69	62.22±18.72	1.057×10^{-1}	No
64702	2	85.71	0.80	0.00	0.00	0.00±0.00	-	No
75202	4	46.67	0.40	100.00	4.56	65.00±23.80	4.935×10^{-9}	Yes
80702	4	46.92	0.80	25.00	0.17	12.50±12.50	4.350×10^{-6}	Yes
81102	2	93.94	0.10	0.00	0.00	0.00±0.00	-	No
85202	2	79.04	0.80	0.00	0.00	0.00±0.00	-	No
93402	2	86.67	0.15	0.00	0.00	0.00±0.00	-	No
93902	3	47.23	0.55	0.00	0.00	0.00±0.00	-	No
94402	4	90.61	0.10	0.00	0.00	0.00±0.00	-	No
95202	4	65.86	0.25	75.00	1.52	51.67±27.34	3.885×10^{-5}	Yes
96002	4	104.20	0.10	0.00	0.00	0.00±0.00	-	No
98102	1	92.17	0.10	0.00	0.00	0.00±0.00	-	No
98202	4	80.00	0.20	75.00	1.04	49.17±22.81	6.058×10^{-7}	Yes
101702	2	76.17	0.30	50.00	1.68	55.00±23.63	-	No
102202	4	50.00	0.90	0.00	0.18	13.33±12.47	-	No
104602	2	80.00	0.10	0.00	0.00	0.00±0.00	-	No
109502	1	34.68	0.35	100.00	0.41	20.00±40.00	5.969×10^{-12}	Yes
110602	2	71.67	0.65	50.00	1.14	38.33±21.15	2.956×10^{-3}	Yes
112802	3	47.43	0.60	66.67	1.28	36.67±21.69	1.646×10^{-8}	Yes
113902	4	53.33	0.55	0.00	0.00	0.00±0.00	-	No
114702	6	60.26	0.85	0.00	0.00	0.00±0.00	-	No
114902	4	40.00	0.10	75.00	2.05	45.83±20.50	9.470×10^{-9}	Yes
123902	2	40.13	0.50	0.00	0.00	0.00±0.00	-	No
Avg				32.64	0.97		**Total**	15

T: firing power threshold; SS_{method}: seizure prediction method sensitivity.; SS_{surr}: surrogate sensitivity; Avg: average.

Table A.13: Testing parameters and performance in the Standard approach with AUC feature selection.

Patient	No. Test Seizures	Preictal (min)	T	SS_{method} (%)	FPR/h	SS_{surr} (%)	P-value	Above Chance
402	2	120.00	0.10	0.00	0.00	0.00±0.00	-	No
8902	2	60.00	0.40	0.00	0.67	20.00±24.49	-	No
11002	2	80.00	0.75	0.00	0.00	0.00±0.00	-	No
16202	4	20.00	0.25	100.00	23.07	60.00±21.98	5.233×10^{-11}	Yes
21902	1	60.00	0.40	0.00	0.00	0.00±0.00	-	No
23902	2	20.00	0.10	100.00	5.48	33.33±32.49	3.267×10^{-12}	Yes
26102	1	120.00	0.10	0.00	0.00	0.00±0.00	-	No
30802	5	80.00	0.10	100.00	2.53	64.67±19.10	3.606×10^{-11}	Yes
32702	2	80.00	0.30	100.00	0.60	28.33±24.78	6.323×10^{-16}	Yes
45402	1	120.00	0.20	100.00	1.26	66.67±47.14	3.361×10^{-4}	Yes
46702	2	53.33	0.35	50.00	0.88	30.00±24.49	6.747×10^{-5}	Yes
50802	2	60.00	0.20	50.00	0.22	11.67±21.15	5.691×10^{-11}	Yes
52302	2	26.67	0.45	50.00	6.75	73.33±30.91	-	No
53402	1	40.00	0.40	0.00	2.15	50.00±50.00	-	No
55202	5	80.00	0.55	0.00	0.08	0.00±0.00	-	No
56402	3	86.67	0.10	0.00	0.00	0.00±0.00	-	No
58602	4	80.00	0.15	75.00	2.22	69.17±17.89	4.485×10^{-2}	Yes
59102	2	66.67	0.45	0.00	0.25	36.67±22.11	-	No
60002	3	26.67	0.20	33.33	7.27	60.00±30.31	-	No
64702	2	40.00	0.45	50.00	0.71	20.00±24.49	1.577×10^{-7}	Yes
75202	4	86.67	0.10	0.00	0.00	0.00±0.00	-	No
80702	4	46.67	0.35	50.00	1.01	40.00±22.91	1.289×10^{-2}	Yes
81102	2	93.33	0.10	0.00	0.00	0.00±0.00	-	No
85202	2	86.67	0.10	0.00	0.00	0.00±0.00	-	No
93402	2	120.00	0.10	0.00	0.00	0.00±0.00	-	No
93902	3	93.33	0.25	0.00	0.00	0.00±0.00	-	No
94402	4	93.33	0.10	0.00	0.00	0.00±0.00	-	No
95202	4	20.00	0.15	50.00	0.76	15.83±16.44	2.403×10^{-12}	Yes
96002	4	86.67	0.10	0.00	0.00	0.00±0.00	-	No
98102	2	86.67	0.10	0.00	0.00	0.00±0.00	-	No
98202	4	120.00	0.10	0.00	0.00	0.00±0.00	-	No
101702	2	86.67	0.15	0.00	0.68	38.3±21.15	-	No
102202	4	26.67	0.35	50.00	0.95	20.83±11.33	1.273×10^{-14}	Yes
104602	2	100.00	0.45	50.00	0.00	0.00±0.00	0.000	Yes
109502	2	33.33	0.40	50.00	2.01	50.00±28.87	-	No
110602	2	93.33	0.70	50.00	0.62	0.00±0.00	0.000	Yes
112802	3	86.67	0.10	0.00	0.00	0.00±0.00	-	No
113902	4	53.33	0.15	100.00	0.87	38.33±22.11	1.625×10^{-15}	Yes
114702	6	86.67	0.10	0.00	0.00	0.00±0.00	-	No
114902	4	93.33	0.15	0.00	0.00	0.00±0.00	-	No
123902	2	66.67	0.10	50.00	1.06	41.67±18.63	1.130×10^{-2}	Yes
Avg				30.69	1.51		**Total**	16

T: firing power threshold; SS_{method}: seizure prediction method sensitivity.; SS_{surr}: surrogate sensitivity; Avg: average.

Table A.14: Testing parameters and performance in the Hybrid approach with AUC feature selection.

Patient	No. Test Seizures	Preictal (min)	T	SS_{method} (%)	FPR/h	SS_{surr} (%)	P-value	Above Chance
402	2	120.00	0.10	0.00	0.00	0.00±0.00	-	No
8902	2	51.33	0.15	0.00	0.65	0.00±0.00	-	No
11002	2	20.00	0.90	0.00	0.16	6.67±17.00	-	No
16202	4	34.14	0.90	50.00	0.00	0.00±0.00	0.000	Yes
21902	1	61.41	0.40	0.00	0.47	50.00±50.00	-	No
23902	2	20.00	0.10	100.00	5.51	51.67±39.76	1.797×10^{-7}	Yes
26102	1	84.46	0.10	0.00	0.00	0.00±0.00	-	No
30802	5	80.00	0.10	100.00	2.33	61.33±23.06	3.157×10^{-10}	Yes
32702	2	85.39	0.60	100.00	0.20	40.00±20.00	2.440×10^{-16}	Yes
45402	1	79.67	0.75	0.00	0.00	0.00±0.00	-	No
46702	2	60.73	0.20	50.00	0.59	33.33±23.57	3.361×10^{-4}	Yes
50802	2	78.34	0.40	50.00	0.24	15.00±22.91	2.269×10^{-9}	Yes
52302	1	20.00	0.40	100.00	11.55	50.00±50.00	4.350×10^{-6}	Yes
53402	1	40.00	0.40	0.00	2.16	60.00±48.99	-	No
55202	5	66.87	0.55	20.00	0.00	0.00±0.00	0.000	Yes
56402	3	18.37	0.70	66.67	1.35	23.33±21.34	4.197×10^{-12}	Yes
58602	3	64.61	0.65	0.00	0.29	26.67±13.33	-	No
59102	2	58.81	0.55	0.00	0.00	0.00±0.00	-	No
60002	3	32.74	0.30	66.67	5.44	66.67±25.82	-	No
64702	2	32.38	0.40	0.00	0.50	21.67±24.78	-	No
75202	4	86.67	0.10	0.00	0.00	0.00±0.00	-	No
80702	4	46.92	0.90	0.00	0.00	0.00±0.00	-	No
81102	2	93.94	0.15	0.00	0.00	0.00±0.00	-	No
85202	2	79.04	0.20	50.00	0.00	5.00±15.00	2.440×10^{-16}	Yes
93402	2	120.00	0.10	0.00	0.00	0.00±0.00	-	No
93902	3	47.23	0.50	0.00	0.00	0.00±0.00	-	No
94402	4	90.61	0.10	0.00	0.00	0.00±0.00	-	No
95202	4	79.19	0.65	0.00	0.00	0.00±0.00	-	No
96002	4	104.20	0.10	0.00	0.00	0.00±0.00	-	No
98102	1	92.17	0.10	0.00	0.00	0.00±0.00	-	No
98202	4	120.00	0.10	0.00	0.00	0.00±0.00	-	No
101702	2	76.17	0.40	50.00	0.77	45.00±15.00	4.154×10^{-2}	Yes
102202	4	70.00	0.75	0.00	0.00	0.00±0.00	-	No
104602	2	100.00	0.45	50.00	0.00	0.00±0.00	0.000	Yes
109502	1	41.34	0.70	100.00	0.00	0.00±0.00	0.000	Yes
110602	2	65.00	0.35	100.00	1.92	63.33±36.36	3.839×10^{-6}	Yes
112802	3	60.77	0.45	66.67	0.73	36.67±21.69	1.646×10^{-8}	Yes
113902	4	53.33	0.15	100.00	0.85	33.33±18.63	2.254×10^{-18}	Yes
114702	6	60.26	0.80	0.00	0.00	0.00±0.00	-	No
114902	4	93.33	0.15	0.00	0.00	0.00±0.00	-	No
123902	2	80.13	0.10	0.00	0.00	0.00±0.00	-	No
Avg				29.76	0.87		**Total**	16

T: firing power threshold; SS_{method}: seizure prediction method sensitivity.; SS_{surr}: surrogate sensitivity; Avg: average.

Table A.15: Testing parameters and performance in the Standard approach with feature-target correlation feature selection.

Patient	No. Test Seizures	Preictal (min)	T	SS_{method} (%)	FPR/h	SS_{surr} (%)	P-value	Above Chance
402	2	120.00	0.10	0.00	0.00	0.00±0.00	-	No
8902	2	53.33	0.15	50.00	0.72	31.67±30.23	1.402×10^{-3}	Yes
11002	2	80.00	0.75	0.00	0.00	0.00±0.00	-	No
16202	4	26.67	0.30	50.00	10.60	61.67±23.92	-	No
21902	1	120.00	0.10	100.00	0.00	0.00±0.00	0.000	Yes
23902	2	26.67	0.15	100.00	2.57	53.33±28.67	6.018×10^{-10}	Yes
26102	1	120.00	0.10	0.00	0.00	0.00±0.00	-	No
30802	5	80.00	0.35	60.00	0.18	14.67±8.84	1.136×10^{-22}	Yes
32702	2	80.00	0.25	100.00	0.67	43.33±17.00	1.496×10^{-17}	Yes
45402	1	20.00	0.30	100.00	27.24	66.67±47.14	3.361×10^{-4}	Yes
46702	2	40.00	0.35	50.00	1.72	46.67±28.67	2.681×10^{-1}	No
50802	2	60.00	0.25	50.00	0.22	25.00±25.00	4.350×10^{-6}	Yes
52302	2	86.67	0.10	0.00	0.00	0.00±0.00	-	No
53402	1	60.00	0.10	100.00	1.75	50.00±50.00	4.350×10^{-6}	Yes
55202	5	73.33	0.20	60.00	0.61	35.33±18.39	2.972×10^{-8}	Yes
56402	3	86.67	0.10	0.00	0.00	0.00±0.00	-	No
58602	4	80.00	0.15	75.00	1.04	50.00±19.36	6.073×10^{-8}	Yes
59102	2	80.00	0.35	0.00	0.29	30.00±24.49	-	No
60002	3	66.67	0.10	100.00	1.95	61.11±24.47	9.950×10^{-10}	Yes
64702	2	86.67	0.10	0.00	0.00	0.00±0.00	-	No
75202	4	86.67	0.10	25.00	0.76	37.50±14.07	-	No
80702	4	46.67	0.60	25.00	0.29	17.50 ±17.26	1.319×10^{-2}	Yes
81102	2	86.67	0.10	0.00	0.00	0.00±0.00	-	No
85202	2	86.67	0.10	0.00	0.00	0.00±0.00	-	No
93402	2	20.00	0.75	0.00	0.15	0.00±0.00	-	No
93902	3	93.33	0.25	0.00	0.00	0.00±0.00	-	No
94402	4	86.67	0.10	0.00	0.11	7.50±11.46	-	No
95202	4	20.00	0.20	25.00	0.66	11.67±19.08	3.781×10^{-4}	Yes
96002	4	20.00	0.25	0.00	3.51	41.67±29.11	-	No
98102	2	120.00	0.10	0.00	0.00	0.00±0.00	-	No
98202	4	66.67	0.30	100.00	1.74	56.67±22.30	1.165×10^{-11}	Yes
101702	2	86.67	0.10	0.00	0.00	0.00±0.00	-	No
102202	4	26.67	0.45	0.00	0.68	17.50±11.46	-	No
104602	2	106.67	0.35	50.00	0.00	0.00±0.00	0.000	Yes
109502	2	86.67	0.10	0.00	0.30	26.67±24.94	-	No
110602	2	66.67	0.35	100.00	0.90	15.00±22.91	8.465×10^{-19}	Yes
112802	3	86.67	0.10	0.00	0.00	0.00±0.00	-	No
113902	4	53.33	0.30	25.00	0.09	0.00±0.00	0.000	Yes
114702	6	20.00	0.55	16.67	0.68	15.00±13.84	2.609×10^{-1}	No
114902	4	86.67	0.70	0.00	0.00	0.00±0.00	-	No
123902	2	73.33	0.15	50.00	0.72	45.00±15.00	4.154×10^{-2}	Yes
Avg				34.43	1.47		**Total**	18

T: firing power threshold; SS_{method}: seizure prediction method sensitivity.; SS_{surr}: surrogate sensitivity; Avg: average.

Table A.16: Testing parameters and performance in the Hybrid approach with feature-target correlation feature selection.

Patient	No. Test Seizures	Preictal (min)	T	SS_{method} (%)	FPR/h	SS_{surr} (%)	P-value	Above Chance
402	2	120.00	0.10	0.00	0.00	0.00±0.00	-	No
8902	2	51.33	0.15	0.00	0.64	0.00±0.00	-	No
11002	2	20.00	0.85	0.00	0.16	3.33±12.47	-	No
16202	4	34.14	0.90	50.00	0.00	0.00±0.00	0.000	Yes
21902	1	48.08	0.40	0.00	0.00	0.00±0.00	-	No
23902	2	26.67	0.15	100.00	2.57	46.67±33.99	1.303×10^{-9}	Yes
26102	1	84.46	0.10	0.00	0.00	0.00±0.00	-	No
30802	5	80.00	0.35	60.00	0.16	18.00±13.01	3.547×10^{-17}	Yes
32702	2	85.39	0.60	100.00	0.20	38.33±21.15	5.122×10^{-16}	Yes
45402	1	79.67	0.65	0.00	0.00	0.00±0.00	-	No
46702	2	27.39	0.15	50.00	0.68	20.00±24.49	1.577×10^{-7}	Yes
50802	2	78.34	0.50	50.00	0.00	0.00±0.00	0.000	Yes
52302	2	86.67	0.10	0.00	0.00	0.00±0.00	-	No
53402	1	60.00	0.10	100.00	1.75	43.33±49.55	5.165×10^{-7}	Yes
55202	5	66.87	0.55	0.00	0.00	0.00±0.00	-	No
56402	3	85.03	0.10	0.00	0.00	0.00±0.00	-	No
58602	3	57.94	0.75	0.00	0.13	24.44±14.74	-	No
59102	2	85.47	0.35	0.00	0.30	25.00±25.00	-	No
60002	3	32.74	0.35	66.67	3.41	50.00±23.96	3.969×10^{-4}	Yes
64702	2	92.38	0.60	0.00	0.00	0.00±0.00	-	No
75202	4	86.67	0.10	25.00	0.76	39.17±15.39	-	No
80702	4	46.92	0.70	25.00	0.08	8.33±11.79	1.069×10^{-8}	Yes
81102	2	93.94	0.10	0.00	0.00	0.00±0.00	-	No
85202	2	79.04	0.25	0.00	0.20	15.00±22.91	-	No
93402	2	20.00	0.75	0.00	0.18	0.00±0.00	-	No
93902	3	47.23	0.50	0.00	0.00	0.00±0.00	-	No
94402	4	90.61	0.15	0.00	0.00	0.00±0.00	-	No
95202	4	45.86	0.50	0.00	0.10	4.17±9.32	-	No
96002	4	37.53	0.40	50.00	0.25	7.50±11.46	8.465×10^{-19}	Yes
98102	1	92.17	0.10	0.00	0.00	0.00±0.00	-	No
98202	4	66.67	0.30	100.00	1.74	62.50±19.09	9.119×10^{-12}	Yes
101702	2	69.50	0.45	50.00	0.63	23.33±24.94	1.554×10^{-6}	Yes
102202	4	70.00	0.75	0.00	0.00	0.00±0.00	-	No
104602	2	106.67	0.35	50.00	0.00	0.00±0.00	0.000	Yes
109502	1	68.01	0.15	0.00	0.53	26.67±44.22	-	No
110602	2	58.33	0.30	100.00	1.01	35.00±22.91	1.047×10^{-15}	Yes
112802	3	40.77	0.55	33.33	1.10	27.78±21.23	8.468×10^{-2}	No
113902	4	53.33	0.30	25.00	0.09	0.00±0.00	0.000	Yes
114702	6	60.26	0.80	0.00	0.00	0.00±0.00	-	No
114902	4	86.67	0.70	0.00	0.00	0.00±0.00	-	No
123902	2	13.47	0.90	0.00	0.60	16.67±23.57	-	No
Avg				25.24	0.42		**Total**	15

T: firing power threshold; SS_{method}: seizure prediction method sensitivity.; SS_{surr}: surrogate sensitivity; Avg: average.

A.3 Visual Inspection of R-R Interval Series and Features

In order to draw some conclusions about the use of unsupervised learning methodologies to determine the preictal interval, a visual inspection of R-R Intervals and features was carried out. The aim of this analysis was to understand if there were alterations in the R-R Interval series for each seizure and whether such changes were reflected in the features. The complete results of this analysis are presented in Table A.17, where we specified which features present alterations.

In summary, it was important to understand if it was possible to find acceptable clustering solutions for the seizures for which alterations were visually detected. Figure A.1 depicts in colours whether or not clustering solutions were accepted, while the diamond means that it was possible to visualize alterations.

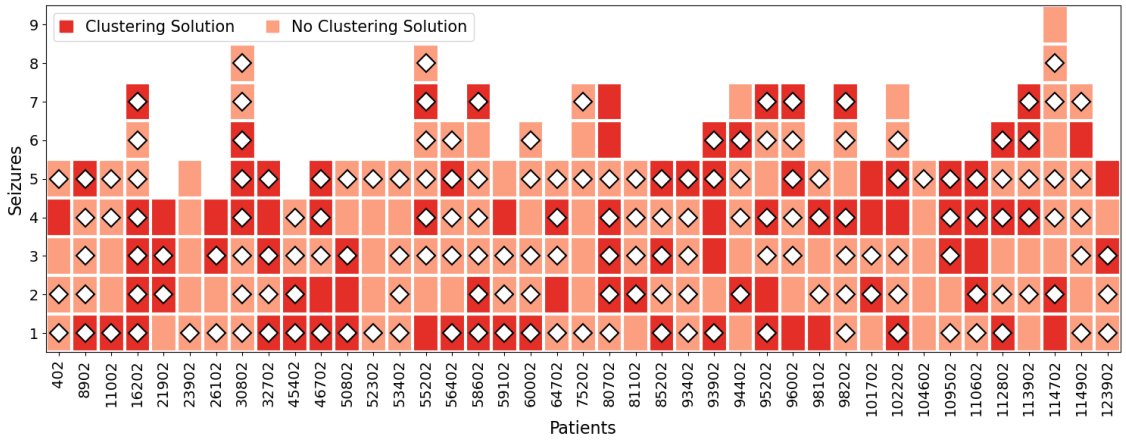

Figure A.1: Representation of the seizures with and without accepted clustering preictal solutions in comparison with the results of the visual inspection of features and R-R Intervals. The colour scale indicates whether clustering solutions were accepted for each seizure. The diamond represents seizures for which it was possible to visualize alterations.

Visual inspection revealed alterations for 168 (70.6%) of the 238 seizures. Earlier, it was mentioned that the unsupervised learning approach yielded solutions for 97 (41%) [22]. Out of these 97 seizures, alterations were found visually for 72. Thus, there are 25 seizures for which clustering preictals were found but no alterations could be found in the visual inspection. This may be simply due to human error in analyzing the seizure data. However, it should be considered that the information analyzed was not the same, since the clustering analysis focused on the feature data and the visual inspection on the R-R Interval series (feature data is only analyzed if there are alterations in the R-R Interval series). This fact can

also account for differences in the results. Additionally, it is also possible that the clustering analysis mistakenly identified noise samples, for instance, as the preictal interval.

There are also 96 seizures for which changes were visualized but no clustering solution was accepted. This is likely related to the fact that the study was limited to searching for solutions comprised of two clusters, while such alterations might be better reflected in solutions with higher numbers of clusters. Thus, a future step would be to perform a more complete clustering analysis, considering solutions with various numbers of clusters.

Table A.17: Results of the visual inspection of the R-R Intervals and features. For each seizure, the intervals during which there are alterations in the R-R Interval are stated, and which features (if any) show alterations during such intervals. Yes means that the majority of features display alterations. The inspection focuses only on the 120-0 min before seizure onset.

Patient	Seizure	Onset Time	R-R Interval (min before onset)	Time-domain Features	Frequency-domain Features	Non-linear Features
402	1	22h45	92-82	Yes	-	DFA (α_1 & α_2), RQA (Ent TT)
	2	21h27	15-0	Yes	LF/HF	-
	3	02h13	-	-	-	-
	4	08h53	Noise in 92-0	-	-	-
	5	08h57	Noise in 45-0; 80-71	Yes	Yes	Yes
8902	1	23h51	80-50	-	LF, LFn, LF/HF	DFA (α_1 & α_2), LLE
	2	23h03	55-24	-	LF/HF	DFA α_1, LLE
	3	05h37	65-50	-	VLF, TP	Yes
	4	00h35	80-50	-	LF, LFn, LF/HF	DFA (α_1 & α_2), LLE
	5	05h10	66-51	Yes	TP, VLF, HF	Yes
11002	1	00h00	100-0	RRMean, RRMin, RRMax	HF, LF/HF	Yes
	2	06h38	-	-	-	-
	3	15h16	-	-	-	-
	4	08h18	50-0	Yes	Yes	Yes
	5	15h40	66-33	Yes	-	SD1, SD2
16202	1	04h34	86-0	Yes	Yes	Yes
	2	06h05	70-60, 27-7	Yes	Yes	Yes
	3	05h07	20-0	Yes	Yes	Yes
	4	18h48	66-15	RRMean, RRMax	LF/HF	LLE
	5	03h34	7-0	Yes	Yes	Yes
	6	13h50	91-80, 25-15	Yes	-	-
	7	19h27	41-0	Yes	HF, LF/HF	SD1, SD2, DFA α_2, RQA (L Ent)
21902	1	16h16	-	-	-	-
	2	08h40	58-0	Yes	LF, HF, LF/HF	Yes
	3	20h32	58-0	RRMean	LF/HF	-
	4	06h50	-	-	-	-
23902	1	10h18	153-0	Yes	LF, HF, LF/HF	SD1, DFA α_1
	2	20h50	Noise in 47-32	-	-	-
	3	11h18	Noise in 40-29	-	-	-
	4	16h48	-	-	-	-
	5	22h17	-	-	-	-
26102	1	15h31	27-0	Yes	LF, HF, LFn, HFn	Yes
	2	08h33	-	-	-	-
	3	07h52	62-0	Yes	LF, HF	SD1, SD2
	4	11h36	-	-	-	-

TP: Total Power; VLF: VLF Power; LF: LF Power; HF: HF Power; LF_n: LF Norm; HF_n: HF Norm.

Table A.17: Results of the visual inspection of the R-R Intervals and features.

Patient	Seizure	Onset Time	R-R Interval (min)	Time-domain Features	Frequency-domain Features	Non-linear Features
30802	1	04h33	32-23	Yes	LF/HF	Yes
	2	04h52	160-94	NN50, pNN50, SDSD, RMSSD	LF, HF	SD1, SD1/SD2, RQA L^{max}
	3	10h58	40-9	Yes	HF, LFn, HFn, LF/HF	SD1, SD1/SD2, DFA (α_1 & α_2), LLE
	4	22h58	15-0	Yes	LF, LF/HF	SD2, DFA α_1
	5	05h49	90-78	Yes	HF, LF/HF	SD1, SD2, LLE
	6	02h48	87-75, 15-0	Yes	Yes	Yes
	7	07h48	82-35	SDNN, RRMean, RRMin, RRVar	Yes	Yes
	8	03h15	32-0	pNN50, NN50, RMSSD, SDSD, RRMean	LF, HF	SD1, DFA α_1
32702	1	08h25	95-85	SDNN, RRMean, RRVar	TP, VLF	SD2, SD1/SD2, ApEn, SampEn
	2	10h22	140-0	RRMean, RRMax, RRVar	Yes	SD1, SD2, ApEn, SampEn
	3	10h13	131-0	Yes	Yes	SD1, ApEn, SampEn
	4	17h03	-	-	-	-
	5	09h29	90-0	Yes	LF, HF, LF/HF	Yes
45402	1	01h48	100-95, 26-20	Yes	Yes	Yes
	2	08h11	Noise in 38-34, 16-10; 34-0	NN50, pNN50, SDSD, RMSSD	HF	SD1, SD2, CD
	3	14h56	130-96	Yes	LF, HF, LF/HF	SD1, SD2
	4	15h13	16-0	Yes	Yes	SD1, SD2
46702	1	15h56	120-108	Yes	LF, HF	SD1
	2	06h16	-	-	-	-
	3	17h06	53-0	Yes	Yes	Yes
	4	02h02	33-7	Yes	LF, HF, LF/HF	Yes
	5	06h45	Gradual increase in HRV; 67-37, 8-0	Yes	Yes	Yes
50802	1	02h44	60-0	Yes	HF, LF, LF/HF	Yes
	2	06h37	-	-	-	-
	3	12h39	45-30	Yes	Yes	Yes
	4	22h50	-	-	-	-
	5	01h18	96-19	Yes	LF/HF	SD1, DFA α_1
52302	1	06h29	20-0	NN50, pNNN50, RMSSD, SDSD	-	Yes
	2	11h31	Noise in 98-73	-	-	-
	3	16h27	-	-	-	-
	4	02h31	Very noisy	-	-	-
	5	09h53	Noise in 24-4; 75-62	NN50, pNN50, RRMean, RRMin	-	-
53402	1	19h09	155-120	Yes	LF, HF	SD1, SD2
	2	08h16	50-0	Yes	LF, HF, LF/HF	SD1, SD2, SD1/SD2
	3	05h46	108-60	NN50, pNN50	LF, HFn, LF/HF	Yes
	4	19h02	Very noisy	-	-	-
	5	09h17	108-10	Yes	LF, HF, LF/HF	SD1, SD/SD2, RQA Rec
55202	1	07h02	-	-	-	-
	2	09h55	No HRV in 48-0	-	-	-
	3	18h15	84-78, 56-32	Yes	Yes	Yes
	4	08h09	52-0	NN50, pNN50, RMSSD, SDSD, RRMean	HF	Yes
	5	17h47	90-68	Yes	Yes	Yes
	6	09h57	129-0	RMSSD, SDSD, RRMean, RRMax	HF, LF/HF	SD1, SD1/SD2, DFA α_1
	7	15h34	Very noisy; 34-21	RRMean	-	-
	8	14h11	17-0	Yes	LF/HF	SD2, DFA α_1, RQA Rec
56402	1	08h17	103-87, 54-0	Yes	LF, HF, LFn, HFn	Yes
	2	21h11	-	-	-	-
	3	01h30	62-57	Yes	Yes	Yes
	4	09h13	62-0	Yes	Yes	Yes
	5	06h29	126-67, 20-0	Yes	Yes	Yes
	6	10h47	Gradual increase in HRV	Yes	Yes	-

TP: Total Power; VLF: VLF Power; LF: LF Power; HF: HF Power; LF_n: LF Norm; HF_n: HF Norm.

Table A.17: Results of the visual inspection of the R-R Intervals and features.

Patient	Seizure	Onset Time	R-R Interval (min)	Time-domain Features	Frequency-domain Features	Non-linear Features
58602	1	09h11	35-0	Yes	LF, HF, LF/HF	Yes
	2	03h29	65-24	Yes	LF, HF, LF/HF	Yes
	3	19h52	56-0	Yes	HF, LF/HF	Yes
	4	09h01	25-0	RMSSD, SDSD, RRMean, RRMin, RRMax	LF/HF	DFA α_1, LLE, RQA L^{max}
	5	15h41	Gradual increase in HRV	Yes	LF, HF, LF/HF	Yes
	6	20h06	-	-	-	-
	7	02h31	31-0	NN50, pNN50	Yes	Yes
59102	1	08h54	Noise in 96-75; 51-23	RRMean, RRmin	LFn, HFn	Yes
	2	15h41	50-0	RMSSD, SDSD, RRMean, RRMax, RRVar	-	-
	3	09h56	Noise in 70-53; 17-0	Yes	LF, HF, LF/HF	Yes
	4	19h51	-	-	-	-
	5	21h12	-	-	-	-
60002	1	02h45	50-46, 7-0	Yes	Yes	Yes
	2	02h22	33-17	Yes	Yes	Yes
	3	12h21	71-50, 19-0	Yes	Yes	Yes
	4	05h40	-	-	-	-
	5	00h17	60-7	Yes	Yes	Yes
	6	22h18	96-66	Yes	Yes	Yes
64702	1	13h53	115-50	Yes	TP, VLF, LF/HF	Yes
	2	04h23	-	-	-	-
	3	18h59	123-97	Yes	HF, LF/HF	Yes
	4	19h50	112-93	Yes	LF, HF, LF/HF	Yes
	5	03h41	88-120	Yes	LF, HF	SD1
75202	1	23h37	67-46, 31-26	Yes	Yes	Yes
	2	01h10	-	-	-	-
	3	21h33	-	-	-	-
	4	19h27	-	-	-	-
	5	09h46	Noise in 94-83; 160-0	Yes	LF, HF, LF/HF	SD1, DFA α_1
	6	17h43	-	-	-	-
	7	06h25	105-83	Yes	-	SD1, DFA α_1
80702	1	05h03	64-42, 22-0	NN50, pNN50, RMSSD, SDSD, RRMean	Yes	Yes
	2	08h43	27-0	RMSSD, SDSD, RRMean, RRMin, RRMax	LF/HF	Yes
	3	20h43	98-76	NN50, pNN50, EMSSD, SDSD, RRMean	HF, LF/HF	Yes
	4	07h46	13-0	RMSSD, SDSD, RRMean	LFn, HFn, LF/HF	Yes
	5	12h27	35-0	RMSSD, SDSD, RRMean, RRMax	HF, LF/HF	SD1, DFA (α_1 & α_2)
	6	17h54	-	-	-	-
	7	08h53	No HRV in 47-0			
81102	1	20h48	-	-	-	-
	2	01h05	108-50	NN50, pNN50, RMSSD, SDSD, RRMean	LF, HF, LFn, HFn	Yes
	3	10h30	150-0	RMSSD, SDSD, RRMean, RRMin, RRMax	LF, LF/HF	SD1, SD1/SD2, DFA α_1
	4	10h44	Noise in 130-113; 145-112	Yes	LF, HF, LF/HF	SSD1, DFA α_1
	5	10h42	167-0	Yes	LF, HF	SD1
85202	1	23h37	124-106	SDNN, RRMean, RRmin, RRMax, RRVar	Yes	Yes
	2	16h51	53-29	Yes	Yes	Yes
	3	04h24	46-0	Yes	Yes	Yes
	4	16h08	137-71	RMSSD, SDSD, RRMean, RRVar	LF, LF/HF	Yes
	5	01h51	30-0	Yes	Yes	SD1, SD2, DFA (α_1 & α_2), LLE

TP: Total Power; VLF: VLF Power; LF: LF Power; HF: HF Power; LF_n: LF Norm; HF_n: HF Norm.

Table A.17: Results of the visual inspection of the R-R Intervals and features.

Patient	Seizure	Onset Time	R-R Interval (min)	Time-domain Features	Frequency-domain Features	Non-linear Features
93402	1	22h17	144-104, 46-0	NN50, pNN50, SDNN, RMSSD, SDSD	TP, VLF, LF, HF	Yes
	2	10h21	134-97	NN50, pNN50, RMSSD, SDSD	TP, HF	SD1, SD1/SD2, LLE
	3	23h20	110-89, 27-0	NN50, pNN50, RMSSD, SDSD, RRMean	HF, LF/HF	Yes
	4	00h59	148-106	Yes	LF, HF, LF/HF	Yes
	5	06h26	120-69, 56-0	Yes	LF, HF, LF/HF	Yes
93902	1	08h39	32-0	RRMean, RRMin, RRMax, RRVar	TP, VLF, LF/HF	SD2, SD1/SD2
	2	16h02	-	-	-	-
	3	02h31	-	-	-	-
	4	18h48	Noise in 134-94	-	-	-
	5	04h02	35-0	Yes	TP, VLF, LF, HF	Yes
	6	09h21	81-0	RRMean, RRMin, RRMax	LF/HF	-
94402	1	15h29	-	-	-	-
	2	11h02	Noise in 60-40; 91-0	Yes	TP, VLF, LF, HF	SD1, SD2
	3	18h05	-	-	-	-
	4	01h36	112-0	RRMean, RRMin	LF, LFn, HFn, LF/HF	Yes
	5	16h10	65-26	RRMean, RRMin	HF	SD1, DFA α_1
	6	02h48	38-0	NN50, pNN50, SDNN, RMSSD, SDSD	Yes	Yes
	7	08h16	Noise in 15-0	-	-	-
95202	1	01h29	Noise in 60-38; 32-0	Yes	HF, LF/HF	Yes
	2	15h00	Noise in 123-103	-	-	-
	3	01h35	56-40	Yes	Yes	Yes
	4	14h13	122-0	RMSSD, SDSD, RRMean, RRMax	HF	SD1, SD1/SD2, ApEn, SampEn
	5	23h30	Noise in 76-61	-	-	-
	6	23h55	63-34	RMSSD, SDSD, RRMean	LF/HF	SD1, SD2
	7	00h04	111-0	Yes	-	SD1, SD2, RQA (L Ent)
96002	1	17h10	Noise in 80-0	-	-	-
	2	10h26	-	-	-	-
	3	17h46	195-92, 14-0	Yes	Yes	Yes
	4	00h05	26-0	RMSSD, SDSD, RRMean, RRMin	-	SD1, RQA Ent
	5	00h44	84-77	RRMean, RRMin, RRMax, RRVar	-	SD2
	6	18h57	85-41	RRMean, RRMin, RRMax, RRVar	-	RQA L^{max}
	7	06h20	Noise in 6-1; 25-0	Yes	Yes	Yes
98102	1	07h17	-	-	-	-
	2	18h49	95-75	Yes	LF, HF, LF/HF	Yes
	3	05h18	-	-	-	-
	4	06h11	8-0	Yes	Yes	Yes
	5	04h07	12-0	Yes	LF, LF/HF	SD1, SD1/SD2, DFA α_1
98202	1	04h50	27-0	SDNN, RRMean, RRMin, RRMax	TP, LF, LF/HF	Yes
	2	20h38	85-0	Yes	-	-
	3	07h16	108-0	RRMean, RRMin	LF, LF/HF	SD1/SD2, AppEn, SampEn, LLE
	4	12h16	22-0	Yes	Yes	Yes
	5	01h22	-	-	-	-
	6	07h55	56-0	Yes	HF, LF/HF	LLE
	7	16h57	23-0	RRMean, RRMax	-	-
101702	1	07h35	-	-	-	-
	2	12h29	28-0	RMSSD, SDSD, RRMean, RRMax	LF/HF	SD1, RQA (Det, Ent, Lam)
	3	19h33	135-86, 41-30	RRMean, RRVar	LF/HF	SD1, SD2, CD
	4	07h35	-	-	-	-
	5	07h35	-	-	-	-

TP: Total Power; VLF: VLF Power; LF: LF Power; HF: HF Power; LF_n: LF Norm; HF_n: HF Norm.

Table A.17: Results of the visual inspection of the R-R Intervals and features.

Patient	Seizure	Onset Time	R-R Interval (min)	Time-domain Features	Frequency-domain Features	Non-linear Features
102202	1	22h50	41-0	RMSSD, SDSD, RRMean	LF/HF	-
	2	15h36	Gradual increase in HRV	Yes	HF, LF/HF	SD1, SD1/SD2
	3	05h47	61-17	NN50, pNN50, RMSSD, SDSD	HF, LF/HF	DFA α_1, RQA (Det, L, Ent TT)
	4	22h14	-	-	-	-
	5	14h07	115-100	Yes	HF, LF/HF	SD1
	6	06h16	110-85	Yes	LF, HF, LF/HF	Yes
	7	15h54	-	-	-	-
104602	1	15h35	-	-	-	-
	2	23h46	Very noisy	-	-	-
	3	06h24	-	-	-	-
	4	12h30	-	-	-	-
	5	22h44	51-32	Yes	LF, HF, LF/HF	SD1, DFA α_1
109502	1	10h00	Noise in 74-43; 117-92	pNN50, RRMean	LF2HF	SD1
	2	19h42	-	-	-	-
	3	02h17	40-0	pNN50	HF	SD1
	4	07h56	90-70	RMSSD, pNN50		
	5	10h17	Noise in 83-55; 124-101	Yes	LF/HF	SD1
110602	1	10h20	52-38	-	-	ApEn
	2	17h39	64-52	Yes	HF, LF/HF	SD1
	3	08h30	-	-	-	-
	4	21h34	75-10	Yes	Total, VLF	Yes
	5	11h28	45-0	Yes	Yes	-
112802	1	17h05	61-47	Yes	Yes	SD2
	2	07h49	40-0	Yes	-	-
	3	15h36	-	-	-	-
	4	06h52	18-0	Yes	LFn, HFn	SD1/SD2
	5	11h54	18-0	Yes	-	-
	6	08h39	Decrease in HRV in 120-0	Yes	Yes	Yes
113902	1	23h32	-	-	-	-
	2	16h55	20-15	Yes	HF, LF/HF	SD1, DFA α_1
	3	05h17	-	-	-	-
	4	13h46	57-28	Yes	Yes	SD1, SD2
	5	22h40	108-94	Yes	-	-
	6	10h00	13-0	Yes	-	-
	7	16h53	92-70, 26-16	Yes	Yes	Yes
114702	1	20h52	Very noisy	-	-	-
	2	14h45	Noise in 119-95; 32-18	Yes	Yes	Yes
	3	04h09	-	-	-	-
	4	09h50	Noise in 141-115; 66-41	Yes	LF, HF	SD1
	5	14h27	67-50	Yes	LF, HF, LFn, HFn	Yes
	6	11h03	-	-	-	-
	7	02h21	97-91	SDNN, RRMean, RRMin, RRVar	Yes	Yes
	8	13h27	142-79	RMSSD, SDSD, RRMean, RRMin, RRMax	Yes	Yes
	9	21h04	-	-	-	-
114902	1	08h30	Noise in 34-17; 52-0	Yes	LF/HF	Yes
	2	14h42	-	-	-	-
	3	19h42	116-106	SDNN, RRMean, RRMax	TP, VLF	-
	4	05h59	99-62	RMSSD, SDSD, RRMean, RRMax	HF, LFn, HFn	SD1/SD2, DFA α_1
	5	17h18	96-88, 22-10	RMSSD, SDSD, RRMean	LF, HF	SD1, ApEn, SampEn, RQA Det
	6	11h52	-	-	-	-
	7	09h27	Noise in 108-93; 90-0	Yes	LF, HF, LF/HF	SD1, SD1/SD2, RQA L^{max}

TP: Total Power; VLF: VLF Power; LF: LF Power; HF: HF Power; LF_n: LF Norm; HF_n: HF Norm.

Table A.17: Results of the visual inspection of the R-R Intervals and features.

Patient	Seizure	Onset Time	R-R Interval (min)	Time-domain Features	Frequency-domain Features	Non-linear Features
123902	1	02h52	118-103, 74-48	Yes	Yes	Yes
	2	01h38	69-43, 29-0	Yes	LF, HF	Yes
	3	02h11	89-61	Yes	LF, HF, LF/HF	SD1, ApEn, SampEn, DFA α_1
	4	18h57	-	-	-	-
	5	15h22	Noise in 114-108	-	-	-

TP: Total Power; VLF: VLF Power; LF: LF Power; HF: HF Power; LF_n: LF Norm; HF_n: HF Norm.