Revolutionizing Epilepsy Diagnosis: Development of an Epileptic Seizure Detection Model using ECG Data

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Abstract

This study lines up into a series of previous attempts to build machine learnings models based on heart rate variability (HRV)-features extracted from electrocardiography (ECG) recordings for detecting seizures with the best possible performance in terms of high sensitivity and low false alarm rate. It aims to examine the role of patient-specific parameters and their impact on detection performance as well as which HRV-features used in the broad spectrum of past studies seem effective when used jointly.

From a methodological perspective, the entire study has been conducted in a CRISP-DM-oriented manner. A review of past studies integrating HRV-features set the foundation for constructing a comprehensive feature set based on multiple datasets of medically labeled inpatient ECG recordings. Model implementation was done using a gradient boosting approach with XGBoost and has been evaluated with different experiments such as consideration of pre-seizure time intervals, (non-)usage of patient-specific data or comparison with healthy individuals. Model performance has been analyzed in regards to key metrics like precision/recall and accuracy by considering the confusion matrices, while XGBoost feature importance, permutation importance and SHAP values have been used for feature evaluation.

Results of the best performing model reveal a very good performance of 94 % accuracy (Seizures: 94 % Recall, 81 % Precision; Non-Seizures: 93 % Recall, 98 % Precision) on the available datasets and 95 % accuracy on a healthy reference group. Nevertheless, several limitations like lack of testing in non-clinical scenarios and sparse patient-data do apply.

Introduction

Epilepsy is a chronic neurological disorder affecting approximately 1% of the world's population. It is characterized by recurrent seizures which can vary in severity and frequency. Although there is an increasing number of antiepileptic drugs as well as surgeries available, still around 30% of patients cannot be cured (Yamakawa et al. 2020). A major challenge for people with epilepsy is the unpredictability of seizures. Sudden seizures can lead to injuries and accidents caused by symptoms such as uncontrollable muscle movement or loss of consciousness, affecting the patient's ability to work, drive and overall perform daily activities (Schulze-Bonhage et al. 2010). Therefore, epilepsy significantly impacts a person's quality of life.

Prediction as well as the detection of seizures are important goals in managing epilepsy, avoiding seizure related injuries and accidents and therefore assist in increasing the security of the patients (Schulze-Bonhage et al. 2010). Additionally, manually maintained seizure diaries by patients and their families are used for monitoring the progress of the disease and the assessment of the effectiveness of treatments. However, these seizure diaries have proven to be unreliable, calling likewise for automatic logging of seizures (Vandecasteele et al. 2017).

When it comes to detecting epileptic seizures, video-electroencephalography (EEG) monitoring is seen as the gold standard by placing electrodes on the head to measure electrical activity in the brain (Van de Vel et al. 2016). However, non-clinical EEG-based approaches require patients to wear costly, eye-catching headsets or brain implants (Cogan et al. 2017).

Recent research has shown that epileptic seizures impact cardiac activity in terms of varying heart rate during and around seizures. This is induced by the neural activations that affect the central atonomic network which is in turn reflected by HRV (Cygankiewicz and Zareba 2013; Jansen and Lagae 2010).

ECG-based data was found to deliver reliable approaches to detect seizures based on HRV (Keilson et al. 1989; Opherk et al. 2002) and can be monitored through less stigmatizing and medically risky hardware

such as small wearables like smartwatches (Cogan et al. 2017; Vandecasteele et al. 2017). These devices are non-invasive and thus have very little physical disruption to patients' normal daily activities (Gagliano et al. 2020). Therefore, it is of great interest to explore the possibility to predict and detect seizures using ECG recordings.

Problem

Using ECG data to detect and predict seizures by using machine learnings models has been already investigated in various studies (Billeci et al. 2018; De Cooman et al. 2018; Fujiwara et al. 2016; Jeppesen et al. 2019; Vandecasteele et al. 2017; Yamakawa et al. 2020; Zambrana-Vinaroz et al. 2022). A recent literature review from van Westrhenen et al. (2019), summarizing studies on seizure detection by evaluating heart rate (variability) parameters, indicates that especially false alarm rates are rather high even though sensitivity is quite good. This results from the fact that HRV is highly situational dependent (Bernardi et al. 2000) and can be affected by patient-specific parameters such as applied treatment (Jansen and Lagae 2010; Persson et al. 2007). Nevertheless, high false alarm rates lead not only to incorrect seizure diaries and verification of treatment effects, but also to reduced meaningfulness for patients.

Till now, there was no study carried out on building machine learnings models by considering a large comprehensive set of HRV-parameters together with patient-specific attributes.

Research Question

In our research project we aim to answer the question whether it is possible to use ECG signals to successfully detect seizures of patients with high sensitivity and low false positive rate by leveraging gradient boosting as machine learning technique. The implementation objective is to develop at least two machine learning models, one with and one without patient-specific features, and to compare their performance using different metrics. These models will be trained and tested on ECG data of epilepsy patients recorded in clinics. Additionally, we aim to provide insights into the impact of different HRV-features extracted from the ECG signals on the classification performance and therefore provide information about the importance of different features. Given that, we define the following research questions:

RQ1: Which HRV-features are showing high positive contribution to the model performance for a gradient boosting-based seizure detection approach?

RQ2: Which patient-specific features are effective in enhancing the model performance for a gradient boosting-based seizure detection approach using HRV?

Approach

For our research project we use the Cross Industry Standard Process for Data Mining (CRISP-DM). It was introduced by Rüdiger Wirth and Jochen Hipp in 2000 and provides a structured approach for data mining projects. To leverage the CRISP-DM methodology we translate our initial medical problem of detecting seizures into a data mining task. The framework is described as a hierarchical process which consists of four levels of abstraction (Wirth and Hipp 2000). The phase level organizes the overall process into a small number of phases. These phases consist of generic tasks which are broken down into more specialized tasks that define the specific actions to be taken (Wirth and Hipp 2000). In our case we have the generic task of building a machine learning model to detect seizures using ECG data. We take this generic task and break it down into tasks such as splitting the data into a test, validation and train set and to perform grid search to find optimal hyperparameters for a better predictive performance of our model. The last hierarchical level is the process instance level, which is a record of actions, decisions, and results. It is used to keep track of what happened during the execution of the overall process and to document the results of the actions taken (Wirth and Hipp 2000). In CRISP-DM, the sequence of tasks is not strictly defined nor is it sequential. Rather, we have the flexibility to go back to earlier tasks and repeat certain actions based on the knowledge gained throughout the process.

The CRISP-DM consists of the following six phases:

- Business Understanding
- Data Understanding
- Data Preparation
- Modelling
- Evaluation
- Deployment

In our research project, we iteratively go through these. Therefore, we can successively build up our domain knowledge in the field of epilepsy as well as get a better understanding of the data and possible connected challenges such as data quality. We aim to build our initial model early on to use the results and performance of this model as a benchmark to understand the baseline performance and gain insights. Based on these insights, we generate ideas to improve the classification performance. We iterate through the process, making changes and improvements in subsequent iterations. By closely monitoring performance changes and evaluating their impact, we isolate and analyze the causes of these changes. This iterative approach allows us to continually refine our models and strive for the best possible solution for the reliable detection of seizures by using ECG data.

Additionally, a literature review will be accomplished beforehand the implementation as part of the business understanding. As stated before, the goal is to evaluate previous studies on using machine learning methods for ECG-based seizure detection that make use of HRV-features. The outcome shall be insights on what HRV-related features can be principally used and how they performed previously as well as what relevance they have for making accurate detections and predictions. For that, selected databases will be searched by using related terms and references that are cited within relevant papers.

The CRISP-DM methodology provides a useful framework for planning, documenting, and communicating throughout the research project (Wirth and Hipp 2000). It ensures that we follow a structured and systematic approach, allowing us to make informed decisions and keep track of introduced changes and their effects to overall address the medical problem in the most efficient way.

Theoretical Background

This section intends to give a basic understanding on how epilepsy affects cardiac behavior and how it can be measured by making use of ECG to examine heart rate variability.

Seizure Impact on Cardiac Behavior

The autonomic nervous system (ANS) consists of the sympathetic nervous system (SNS), parasympathetic nervous system (PNS) and the enteric nervous system (ENS) (Gibbons 2019). The SNS and PNS are traditionally known to control “fight and flight” and “rest and digest” functions which is why they have different influences on the body functionality: While the SNS predominates during physically demanding situations such as exercising or emergency cases leading to increased heart rates and higher blood pressure, the PNS predominates during resting conditions when the body is prepared to conserve and store energy, leading to the opposite physical condition (Gibbons 2019; McCorry 2007). During seizures, an imbalance between the SNS and PNS can be observed which in turn leads to altered cardiac behavior due to changes in blood pressure or heart rate (Devinsky 2004; Wannamaker 1985). Furthermore, seizures may already affect aspects of the ANS prior to an ictal state (the time from the first symptom to the end of the seizure activity) (Karasmanoglou et al. 2023). In order to measure those changes in heart rate, each heartbeat within a specified time window needs to be identified and considered.

ECG is used to do so, which makes use of electrodes placed on the chest to register electrical activity by measuring changes in the electrical potential difference during depolarization and repolarization of the contractible cardiac muscle cells. Generally, an electrical stimulus is generated by the sinus node – a special cardiac muscle region which is under direct influence of the SNS and PNS (Gacek and Pedrycz 2012) – and causes the heart’s ventricles to contract (Halhuber et al. 1979). Those ventricles in turn are made up of cardiomyocytes that generate electrical potential during contraction as their electrical membrane changes its permeability for positively charged ions. While being normally polarized with a membrane potential of

about -90 mV, an external stimulus such as the sinus node can trigger a reversal of the electrical potential which is known as depolarization (Gacek and Pedrycz 2012; Halhuber et al. 1979).

This regular electrical activity is in turn visible in the ECG as a typical pattern, the so-called QRS-complex (Stroobandt et al. 2015), like illustrated in Figure 1.

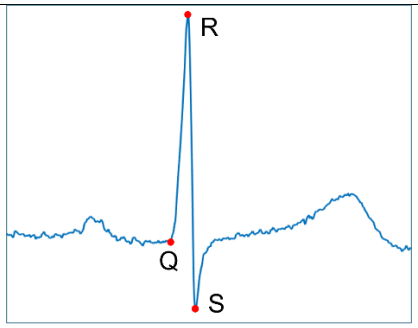


Figure 1. QRS-complex

Depolarization of the transitional zone between the left and right ventricles is represented by the Q-wave and followed by the ventricular depolarization with the positive R-wave and the repolarization with the S-wave (Gacek and Pedrycz 2012; Peters et al. 2009). At this point in time, blood will be ejected from the heart which is considered as a single heartbeat (Stroobandt et al. 2015). Measuring heartbeats or calculating heart rate is then done by considering the R wave as a single heartbeat within the QRS-complex and determining the interval between successive R waves, known as R-R interval. In turn, this measurement can be then used to calculate temporal variations between successive heartbeats as depicted in Figure 2 (Petty 2020).

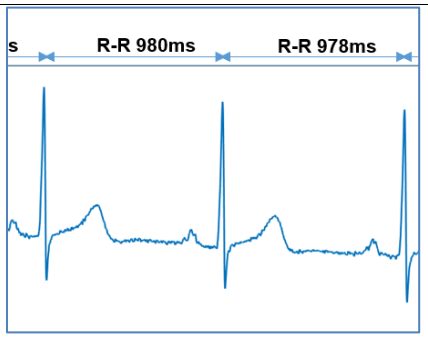


Figure 2. R-R intervals

Those changes between heartbeats are known as HRV and there are numerous methods to measure it which can be distinguished mainly into three categories: Time-domain, frequency-domain and non-linear measurements.

Overview of HRV-parameters

This section gives an overview over frequently used HRV-parameters in past research, comprehensively listed in Table 1. This serves not only as input for the detection model, but also helps in narrowing the amount of senseful input features in alignment with results from feature engineering. For that, several databases have been searched through and backward reference searching has been applied to the identified papers.

The following keywords have been used separately as well as in combination: ‘seizure detection’, ‘epilepsy detection', ‘heart rate variability’, 'HRV’, ‘RRI’, ‘R-peak detection’, ‘machine learning’, ‘QRS’ in the following databases: PubMed (National Institutes of Health), IEEE Xplore, ACM DL, Google (Scholar), ScienceDirect, MDPI, Wiley

	(Jeppesen et al. 2019)	(Jeppesen et al. 2014)	(Jeppesen et al. 2010)	(Jahanbekam et al. 2021)	(Jeppesen et al. 2020)	(Fujiwara et al. 2016)	(Giannakakis et al. 2019)	(Evrengul et al. 2005)	(Massetani et al. 1997)	(Aimaier et al. 2022)	(Smimov et al. 2017)	(Behbahani et al. 2016)	(Behbahani et al. 2014)	(Jeppesen et al. 2023)	(Karasmanoglou et al. 2023)	(Billeci et al. 2018)	(Yamakawa et al. 2020)	(Jeppesen et al. 2015)
AVG				X		X	X				X	X	X		X	X	X	
SDRR				X		X	X	X		X	X				X	X	X	
VAR									X		X					X		
RMSSD				X		X	X	X		X	X				X	X	X	
SKEW															X			
KURT															X			
NNx/NN50				X		X	X				X				X	X	X	
pNNx/pNN50				X			X	X		X						X		
HRV triangular index							X											
CSI	X	X		X												X		X
CSI_SLOPE	X				X									X				
CSI_FILTERED	X																	
CSI_FILTERED_SLOPE	X																	
CSIM	X	X																X
CSIM_SLOPE	X																	
CSIM_FILTERED	X																	
CSIM_FILTERED_SLOPE	X				X									X				
CVI	X	X		X												X		
SD1, SD2		X								X		X	X		X	X		
HR_DIFF	X																	X
HR_DIFF_SLOPE																		
HR_DIFF_FILTERD	X																	
HR_DIFF_FILTERED_SLOPE																		
ULF																		
VLF				X														
LF			X	X		X	X	X	X	X	X	X	X		X	X	X	
HF			X	X		X	X	X	X	X	X	X	X		X	X	X	X
LF/HF-ratio			X	X		X	X	X	X	X	X	X	X		X	X	X	
Total power				X		X	X	X									X	

Table 1. Review of HRV-parameters in literature

Time-domain metrics

Time-domain metrics as listed in Table 2 describe the analysis of HRV by considering the variability between consecutive heartbeats (Hammerle et al. 2020; Jeppesen et al. 2014; Jeppesen et al. 2019; Shaffer and Ginsberg 2017). They focus on analyzing statistical characteristics of R-R intervals in regards of time without taking the frequency components of the ECG signal into account.

Metric name	Unit	Description
AVG	ms	Average of R-R intervals
SDRR	ms	Standard deviation of R-R intervals
VAR	ms	Variance off R-R intervals
RMSSD	ms	Root mean square of successive R-R interval differences
SKEW	-	Skewness of R-R intervals
KURT	-	Kurtosis of R-R intervals
NN50	count (ms)	Number of successive R-R intervals differing by more than 50 ms
pNN50	%	Percentage of NN50
HR_DIFF	ms	Second-order differentiation of consecutive R-R intervals (change of R-R intervals over time)
HRV triangular index	-	Integral of the density of the R-R interval histogram divided by its height
25%-/50%/75%-Quantile	ms	1st quartile/2nd quantile/3rd quantile of the distribution of R-R intervals

Table 2. Time-domain HRV metrics

The "_SLOPE"-variant of HR_DIFF is being calculated by multiplying the slope of the R-R interval values over time within the corresponding time slice to dampen the impact of potential arousals during nighttime on HRV. "_FILTERED"-variant aims on compensating R-peaks that were incorrectly detected (or not all) by calculating the median duration for the previous seven R-R intervals for each heartbeat/R-peak.

Frequency-domain metrics

Frequency-domain metrics as listed in Table 3 split the distribution of signal power into different frequency bands (Őri et al. 1992; Shaffer and Ginsberg 2017) as exemplarily shown in Figure 3.

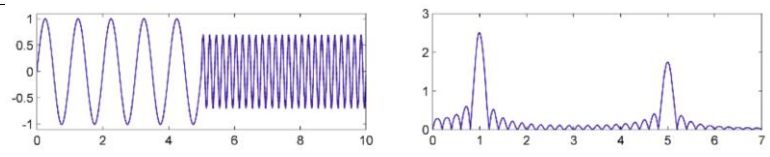


Figure 3. Frequency analysis (Müller 2015)

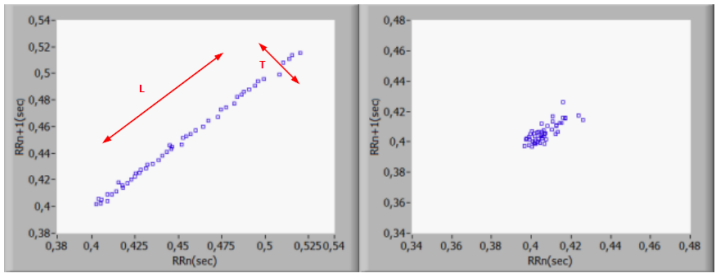
In regards to HRV, past research has shown that correlations between specific frequency bands and physiological activity exist, such as low frequency power originating back to SNS activity while high frequency power is implied by PNS activity (Shaffer and Ginsberg 2017). The conversion of the HRV time series into frequency bands is done by using fast fourier transform in this study.

Metric name	Unit	Description
ULF	ms²	Power of ultra-low-frequency band (0 <= 0.003 Hz)
VLF	ms²	Power of very-low-frequency band (0.003 <= 0.04 Hz)
LF	ms²	Power of low-frequency band (0.04 <= 0.15 Hz)
HF	ms²	Power of high-frequency band (0.15 <= 0.4 Hz)
LF/HF-ratio	-	Ratio of LF-to-HF power
Total power	ms²	Sum of ULF, VLF, LF and HF power

Table 3. Frequency-domain HRV metrics

Non-linear metrics

Non-linear metrics as listed in Table 4 address the uncertainty of the time series which results from the variety of different mechanisms that impact HRV (Shaffer and Ginsberg 2017). A common tool is poincaré analysis which has been used frequently in past studies to quantify irregularities in heart rate. The poincaré plot serves as basis for the analysis, where all RR intervals RRI_i are plotted against the consecutive RR intervals RRI_{i+1} (Jeppesen et al. 2014). The standard deviation SD1 for the transverse direction (T) measures short-term variability while the standard deviation SD2 for the longitudinal direction (L) measures short-term variability as well as long-term variability (Shaffer and Ginsberg 2017). The ratio of both measures autonomic balance and can help indicating different cardiac behavior, as it is shown in Figure 4 for a seizure and non-seizure scenario.



A) Seizure B) Exercise

Figure 4. Poincaré analysis (Jeppesen et al. 2014)

Metric name	Unit	Description
CSI	-	Cardiac Sympathetic Index; calculated by $\frac{SD2}{SD1}$
CSIM	-	Modified CSI; emphasizes SD2 by using $\frac{SD2^2}{SD1}$
CVI	-	Cardiac Vagal Index; calculated by $log_{10}(SD2 * SD1)$
SD1, SD2	ms	Standard deviations for transverse T (SD1) and longitudinal L direction (SD2)

Table 4. Non-linear HRV metrics

Model Foundation

Dataset

The data used in this study, broken down in detail in Table 5, comprises four primary sources: the University Clinic of Tübingen (UCT), the University Clinic of Aachen (UCA) (specifically the epilepsy department), the University Clinic of Freiburg (commercially available data), and a dataset of healthy individuals. The collected dataset consists of ECG recordings from various patients. The seizure onset and offset timestamps were determined and annotated by the respective doctors at the recording centers (clinics). In addition, the dataset includes ECG recordings from healthy individuals, captured during their everyday activities including physically demanding tasks such exercising. The healthy individual dataset was primarily employed to evaluate the model's performance on ECG data from non-seizure cases. Additionally, this study focuses solely on complex partial seizures (CPS).

Recording Center	Number of Patients	Total duration of recordings (hours)	Number of CPS
UCT	146	6.617	291
UCA	659	48.158	379
Freiburg	163	16.591	639
Sandor	17	1.484	30
Healthy	35	1.654	0

Table 5. Dataset overview

Data Preparation

The seizure onset timestamp serves as the starting point for analysis, and subsequent time slices are created. A total of 55 time slices are generated, each spanning 30 seconds in duration. A step size of 5 seconds is used as the intervals between consecutive time slices. For each time slice, the features described in the overview of HRV-parameters earlier are calculated.

For building the training set from the given data, 10 non-seizure ECG time slices per seizure time slice are sampled. Similar to the seizure data, time slices are created from these non-seizure timeframes. The mentioned features are then calculated for each of these non-seizure time slices, following the same methodology described above.

The reason for sampling 10 times more non-seizure time slices than seizure time slices is that it allowed us to be more flexible in adjusting the seizure-to-non-seizure ratio during the model building, analysis, and evaluation steps. It also provided the opportunity to downsample the number of non-seizure data points. By employing this strategy, we aimed to ensure robustness and optimize the performance of our model.

To further enhance the robustness of our model's validation, we performed a dataset split into three distinct subsets: train, test, and validation sets. Considering the patient-specific nature of ECG data, our intention was to prevent the model from recognizing individual patients, thus avoiding potential deceptive model performance and data leakage. The data split was accomplished by randomly assigning a selected number of patients to each subset, ensuring that the data from each patient resided exclusively within a specific data split. By implementing this approach, we maintained the integrity of our validation process and mitigated the risk of bias arising from patient-specific patterns or characteristics.

Model and Metrics

In this study, we employed a gradient boosting model using the XGBoost package for our analysis. Gradient boosting models combine multiple weak predictive models to create a strong ensemble model. It iteratively trains new models to minimize the errors made by previous models, resulting in a highly accurate and robust predictive model capable of capturing complex relationships in the data.

To ensure optimal model performance, we conducted hyperparameter tuning using a grid search approach. This involved systematically exploring various combinations of hyperparameters to identify the configuration that yielded the best results.

For evaluating the performance of our model, we employed multiple metrics. The primary metric of interest was recall, which measures the ability of the model to correctly identify positive cases. Additionally, we assessed accuracy as a measure of overall classification performance. To gain further insights into the model's performance, we examined the respective confusion matrices, which provide a detailed breakdown of true positives, true negatives, false positives, and false negatives. By considering these metrics and the associated confusion matrices, we were able to comprehensively evaluate the effectiveness and robustness of our gradient boosting model.

Experiments

Time Slice-specific Model Performance

To assess the significance of individual time slices and their informative value in classifying seizure and non-seizure cases, we conducted an experiment by independently fitting various gradient boosting models using the 55 different time slices and their respectively calculated features. We then compared the performance of these models to determine the time slices that contributed most effectively to the classification task.

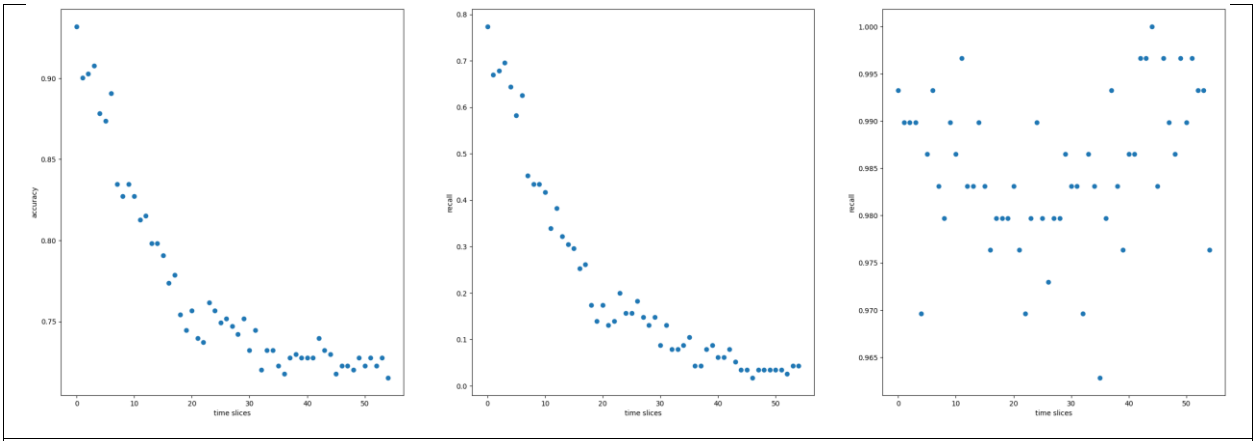


Figure 5. Performance Comparison using individual Time Slices

As seen in Figure 5, the results for the model performance using individual time slices as input reveal that the later time slices yield significantly poorer performance, with most cases being classified as non-seizures. This outcome aligns with our expectations, as seizure periods vary in length, and certain time slices may extend beyond the seizure offset time.

Effect of Pre-Seizure HRV on Model Performance

To investigate the impact of pre-seizure ECG data on the performance of our model, we explore a certain time period prior to the documented seizure onset. Past studies have suggested that changes in heart rate variability can be observed even before a seizure occurs. By considering time periods preceding the seizure onset, we aimed to assess whether incorporating pre-seizure data influences the classification performance of our model. In our experiment we test the model performance on time slices with a starting point 90 seconds before the denoted seizure onset and a step size of 5 seconds.

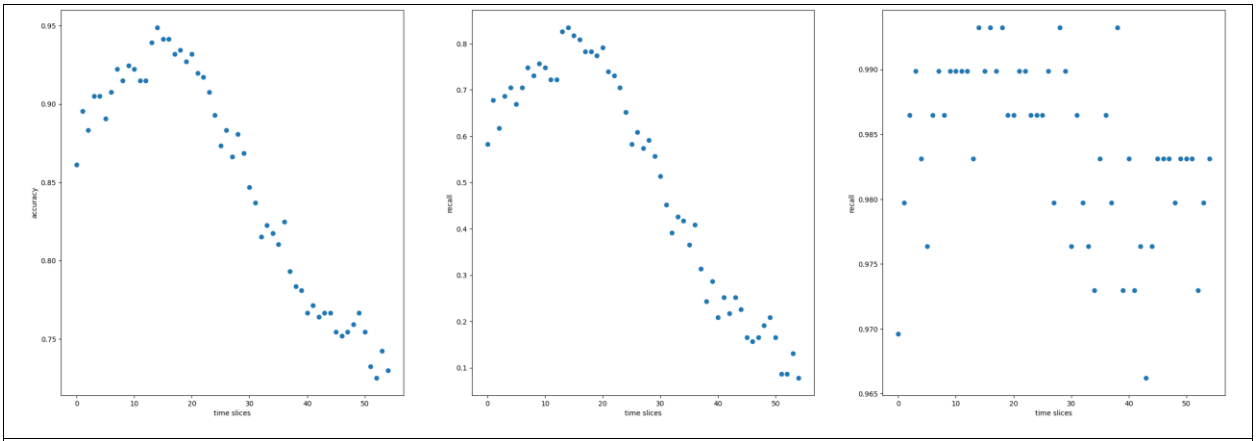


Figure 6. Performance Comparison using Pre-Seizure Time Slices

The results of this experiment illustrated in Figure 6 clearly show a notable decrease in model performance as the time slices move further away from the seizure onset. The peak performance, as indicated by the seizure recall (True-Positive rate), was achieved at the 18th time slice, corresponding to the time slice with the seizure onset as the starting point.

Time slices with a starting point up to 20 seconds (time slices >13) prior to the denoted seizure onset also exhibited strong performance in terms of recall, even surpassing the model with a starting point at the seizure onset for overall accuracy. However, it should be noted that these time slices incorporate data from the actual seizure recording due to the 30-second time slice size. Additionally, imperfect seizure onset annotations could have influenced the results, making it unclear if heart rate variability prior to the actual seizure onset is useful for seizure classification.

Model Performance on Different Data Filter

Tachycardia (precisely sinus tachycardia) is generally defined as the heart rate exceeding 100 beats/min. While this can generally originate from triggers like emotions or physical activity, it is an important vital sign (Gopinathannair and Olshansky 2015). Studies reported that tachycardia is a prominent characteristic for the ictal phase and has also been found during the post-ictal phase (Billeci et al. 2018; Devinsky 2004; Mazzola and Rheims 2021). However, considering tachycardia to imply seizures can be also misleading as it needs to be distinguished from typical daily activities such as physical exercise that impact the ANS and lead to tachycardia as well (Jeppesen et al. 2015).

Given that tachycardia is an indicator for seizures, it is decided to implement the different heart rate filtering mechanisms listed in Table 6 on the training datasets which are then used for improved model training. One filter is built for considering the increasing heart rate alteration and two further filters are used for setting a fixed heart rate threshold. As the heart rate threshold for defining tachycardia is a debated definition (Gopinathannair and Olshansky 2015) and previous studies examined seizures based on different thresholds at around 100 beats/min (Eggleston et al. 2014), it is decided to lower the thresholds to prevent overfiltering.

Filter No.	Description
1	5 % increase in heart rate for ≥ 1 timeslice *i+1* vs. timeslice *i*
2	≥ 1 timeslice with a heart rate ≥ 85
3	≥ 1 timeslice with a heart rate ≥ 90
4 (default)	no filter applied

Table 6. Filter

All three filtering approaches rely on the R-R interval in ms and calculate the heart rate by $\frac{60000\ ms}{RRI\ ms}$. Filter 1 considers only records if a relative increase in heart rate of 5 % between at least one pair of consecutive timeslices exist, i.e. if at least one timeslice *i+1* exists with an increase in heart rate of 5 % to timeslice *i*. Filter 2 and 3 consider only records where at least one timeslice exists that exceeds the respective heart rate threshold.

When we applied the different event filters it was observed that the application of each respective filter did not yield an improvement in the performance of the model. Notably, the optimal performance was consistently retained when no event filters were applied whatsoever.

Effect of the Consideration of Multiple Time Slices

In this experiment, our primary objective was to assess the impact of incorporating a larger number of time slices into our model's input on its overall performance. This approach involves the calculation of the HRV-features individually for each 30-second time slice, followed by the utilization of these metrics from multiple time slices as inputs for the model as opposed to the prior experiments, where single time slices where used. These time slices are again spaced with a step size of five seconds.

To additionally explore potential dimensionality reduction benefits, we initially examined the applicability of principal component analysis (PCA). This was done especially because the incorporation of multiple time slices significantly increased dimensionality. We conducted tests across varying numbers of PCA components, yet counterintuitively, the model's performance experienced a notable decline across the board when employing PCA. This decrease in performance was observed both when applying PCA globally to all time slices and when applying PCA individually to each time slice before utilizing the cumulative components as model inputs.

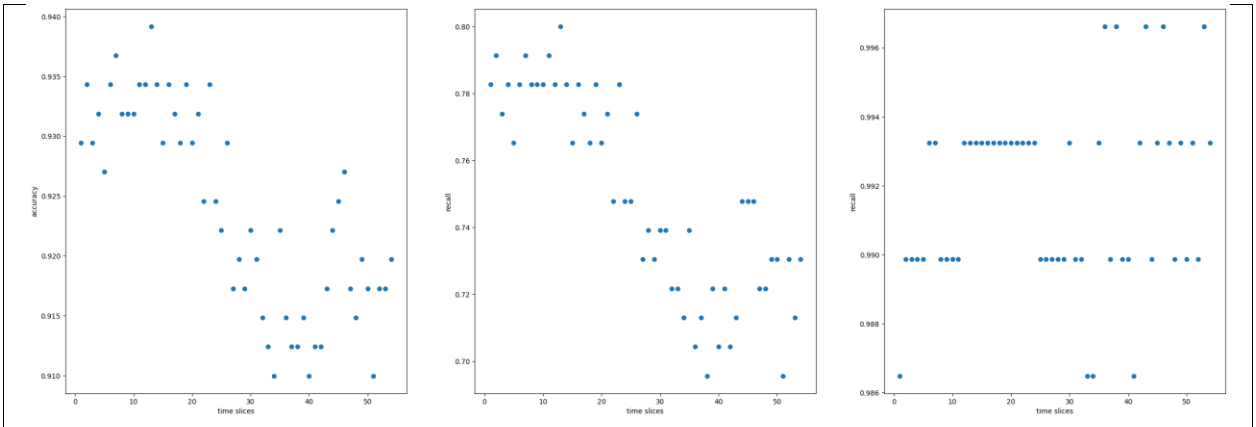


Figure 7. Performance Comparison using multiple Time Slices

Turning our attention to the influence of the amount of time slices as input for the model, we identified a clear pattern. Incorporating a larger quantity of time slices as model inputs exhibits the potential to elevate overall performance, particularly in terms of recall. This trend is evident from the seizure onset through the inclusion of the first 14 time slices, where nearly each additional time slice leads to performance enhancement. Beyond the 14th time slice, however, we can observe that the performance starts to decline again. Consequently, an optimal balance exists in terms of the number of time slices to incorporate as model inputs. We assume that this phenomenon is tied to the capacity to capture a greater volume of information with more time slices. Yet, exceeding a certain time period that often extends beyond the seizure offset leads to encompassing data that may not be distinctly characteristic of a seizure. This subsequently poses challenges for the model in distinguishing between seizure and non-seizure instances.

Analysis of Feature Importance

To assess the significance of features within our model, we employed a comprehensive approach utilizing three key metrics: XGBoost feature importance, permutation importance, and Shapley additive explanations (SHAP). These metrics collectively provide a comprehensive view of the role each feature plays in influencing model predictions.

XGBoost's feature importance in Figure 8 is determined through a metric called information gain. This value gauges the relative contribution of a given feature to the model by quantifying its impact on decision tree construction. Information gain measures the enhancement in prediction accuracy attributed to a feature. Specifically, when a new split is introduced based on a feature, it results in more accurate branches, thereby refining model predictions.

Additionally, permutation importance as illustrated in Figure 9 offers insights into feature significance by evaluating the effect of randomly permuting a feature's values while monitoring the resulting impact on the model's performance. However, permutation importance hinges on the assumption that the employed features have minimal correlation among themselves. A challenge encountered in our analysis was the presence of numerous features characterized by high correlation. In response, we adopted a refined approach to computation. Specifically, we conducted permutation importance calculations for each individual feature while systematically excluding features that demonstrated high correlation with the feature under evaluation.

SHAP values in Figure 10 represent another integral part of our analysis. SHAP values provide a nuanced perspective on feature importance, considering interactions between features. By evaluating how the model performs with and without a particular feature across all possible feature combinations, SHAP values capture the average marginal contribution of a feature value across various scenarios.

As it can be seen especially in the XGBoost feature importance analysis in Figure 8, the poincaré analysis taking short-term and long-term variability of the heart rate into account has an essential role. From a technical perspective, the CSI and CSIM measure autonomic balance of the nervous system and are thus a direct indicator for seizure occurrence. The higher feature importance for CSIM in contrast to CSI could be explained by the emphasis on the overall R-R interval fluctuations (SD2) which tends to have higher variance than the beat-to-beat differences (SD1). This also explains analogous the higher permutation importance due to the sensitivity of the metric for high SD2-values. SD1 and SD2 seem insignificant when considered as separate variables and the filtered- and slope-variants of CSI/CSIM are not leading to any improvements but are getting irrelevant according to their permutation importance.

When considering the frequency-domain, the biomedical background for influences on different frequency bands corresponds as well with the results. The VLF band is highly sensitive according to permutation importance and SHAP values which corresponds with the fact that it is primarily being influenced by SNS activity which is in turn an indicator for ongoing seizures. Nevertheless, it needs to be kept in mind that such activity can also result from physical activity. As the ULF band is said to represent the circadian rhythm, longer timeframes would probably be needed to get some relevance out of it and the LF/HF bands are influenced by the PNS and consequently less influential.

In regards of time-domain, most statistical parameters seem to play a subordinate role. However, the heart rate differential-method depicting increasing and decreasing R-R intervals seems appropriate for

identifying seizures, as already expected by results of past studies. Consequently, measured variance for R-R intervals represented by VAR shows similar importance as differing R-R intervals might be correlated to decreasing/increased HRV represented by HR_DIFF.

The patient-specific features, age and gender (M/F/U), couldn't contribute crucially to the model performance which is seen especially in the feature importance with being ranked in the midfield for age and coming in last for the gender. SHAP values and permutation importance paint a similar picture with no significant impact on the model.

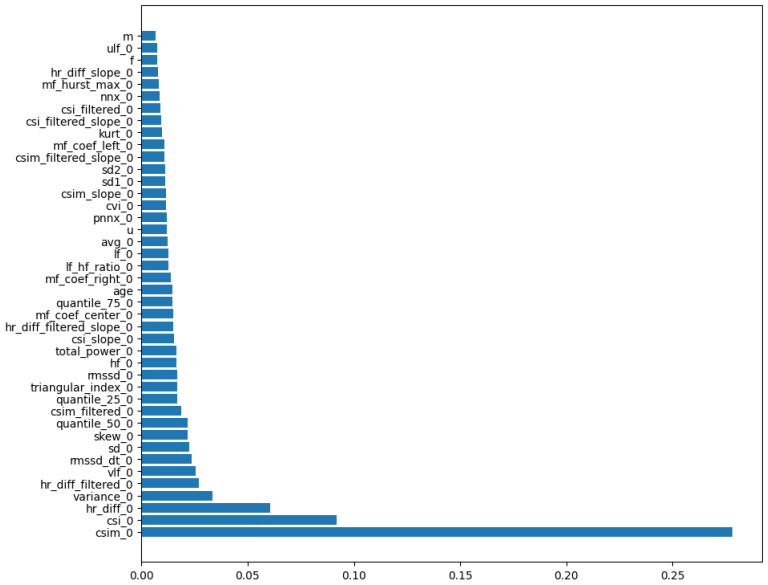


Figure 8. XGBoost Feature Importance

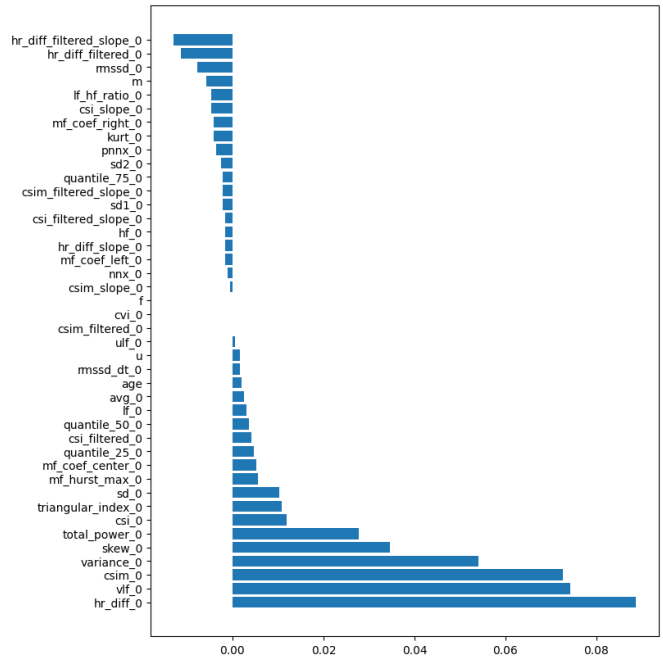


Figure 9. Permutation Importance

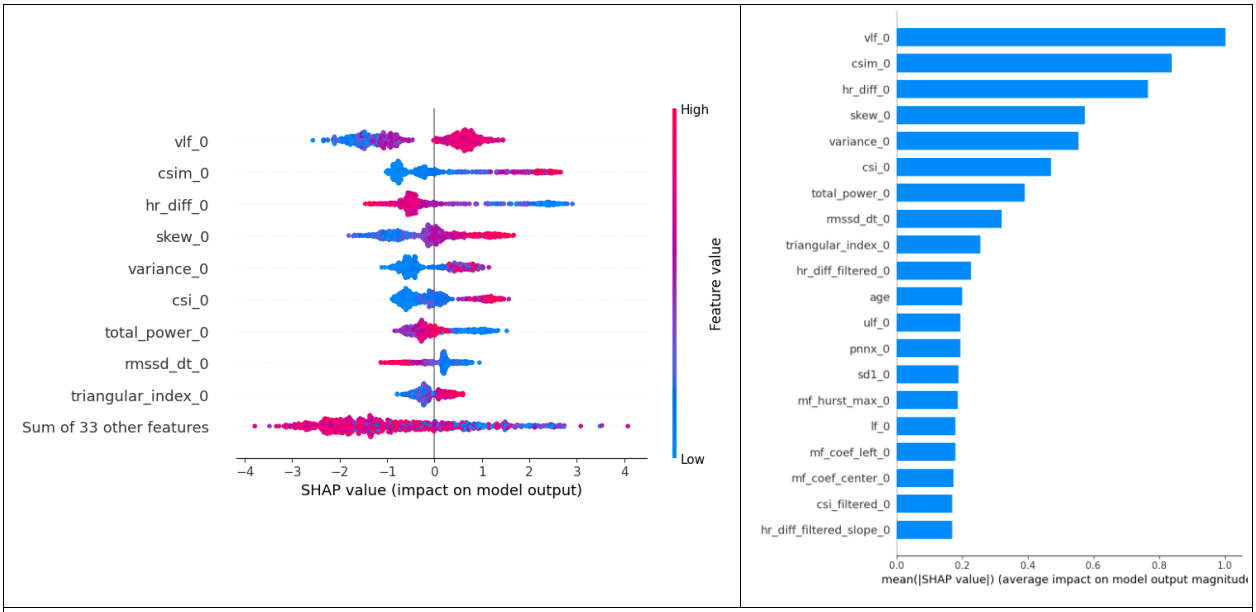


Figure 10. SHAP Values

Evaluation of Model Performance on Healthy Dataset

In order to evaluate the model's ability to discriminate between epileptic seizures and various daily activities conducted by healthy individuals, a distinct dataset was used. This dataset comprised ECG recordings obtained from healthy subjects engaged in diverse daily tasks, including physical exercises. While our XGBoost model was initially trained on patient data acquired within hospital settings, its performance was subsequently evaluated on this healthy population dataset, which does not contain any seizure instances.

Among a randomly selected pool of 2000 recordings from healthy individuals, the model demonstrated a mere 104 instances of misclassification as seizures. This outcome translates to an accuracy rate of 95%. It must be noted that the model's classification threshold remained at the default 50%.

The model used for classification in this experiment was also evaluated on a test set containing seizures. It achieved a recall of 76% and the precision was marked at 92%, underscoring the model's proficiency in accurately labeling seizure instances. The F1-score, a composite measure of precision and recall, stood at 83%.

This experiment presents compelling evidence supporting the hypothesis that the model, originally trained solely on hospital-recorded patient data marked by controlled conditions, extends its effectiveness to real-world scenarios characterized by a diverse array of daily activities. The successful translation of the model's discriminative power to a dataset featuring healthy individuals engaged in routine tasks underscores its potential for practical application beyond clinical environments.

Effect of Patient-Specific Data on Model Performance

To investigate the influence of patient-specific data on the performance of our model, we conduct an experiment considering individual characteristics such as age and gender. Previous studies have highlighted that heart rate variability is patient specific. Therefore, we employed a gradient boosting model that incorporates these patient-specific features to assess their impact on the classification performance of our model.

Initially, the introduction of age and gender as supplementary input features did not yield an improvement in model performance. Contrarily, the model's performance exhibited a slight decrease in performance, particularly in the precision of the seizure class, which decreased from 97% to 96%, and a similar decline in

recall from 81% to 79%. This phenomenon could be attributed to the limited size of the dataset, where the model potentially began associating age and gender with specific patients, leading to overfitting.

Furthermore, the assessment of feature importance underscored the limited influence of age. Across various importance metrics, such as XGBoost feature importance, SHAP importance and permutation importance, age consistently ranked relatively low. It secured the 20th place for XGBoost feature importance, 11th for SHAP importance, and 17th for permutation importance.

To mitigate the potential overfitting concern, an alternative approach was adopted. A model was constructed using age ranges, categorized into five-year intervals, as input features. However, the incorporation of age ranges failed to augment the model's performance beyond that achieved without this feature. Moreover, there was no discernible increase in the significance of age-related features in terms of feature importance. Notably, the gender did not yield an impact on overall performance, displaying negligible relevance in feature importance evaluations.

The evaluation of weight and height as features posed challenges due to substantial missing values, rendering an assessment of model performance incorporating these features unfeasible.

In conclusion, the integration of patient-specific data into the model, encompassing age and gender, did not produce a significant enhancement in performance. The experiment underscored the potential risks of overfitting and reinforced the necessity for careful consideration when incorporating such features into the model's training.

Best achievable Model Performance

In this phase of experimentation, we want to leverage the insights gained from preceding investigations to optimize model performance.

As a foundational input, the model is provided with a sequence of time slices, encompassing four slices preceding the onset of a seizure, in conjunction with a cumulative total of 15 time slices. Additionally, the age range attribute is incorporated as a feature, contributing to the comprehensive feature space for model training. One central adjustment involves the adoption of a distinct prediction threshold, as in prior iterations the prediction probability was not taken into account. This new threshold is set at 0.007, ensuring that predictions of the absence of a seizure are exclusively made when the model has a high level of confidence in this decision.

By leveraging these refined parameters, the model attains a remarkable performance level. For the seizure class, the achieved metrics include a recall of 94% and a precision of 81%. These statistics reflect the model's capability to accurately identify a substantial proportion of actual seizure instances while maintaining a high precision in these predictions. Concurrently, for the non-seizure class, the model has a precision of 98% and a recall of 93% on the test set.

The overarching accuracy of the model lies at 94%.

Discussion and Limitations

In this study we implemented gradient boosting-based machine learning models using XGBoost for seizure detection by using medically labeled inpatient ECG recordings from various clinics with patient-specific data. These recordings were used to derive HRV-features that were gathered in a review from past studies concerning seizure detection based on HRV. This built the foundation for answering our two research questions:

RQ1: Which HRV-features are showing important contribution to the model performance for a gradient boosting-based seizure detection approach?

RQ2: Which patient-specific features are effective in enhancing the model performance for a gradient boosting-based seizure detection approach using HRV?

Our results from conducting several experiments show that the best performing model could reach an accuracy of 94 % (Seizures: 94 % Recall, 81 % Precision; Non-Seizures: 93 % Recall, 98 % Precision) by incorporating all listed HRV-features inclusive age range as patient-specific feature. On a dataset with

exclusively healthy persons recorded at everyday life, a similar accuracy of 95 % could be measured. For using the time slicing method, an interval of four time slices before to 11 time slices after seizure onset was used (-20 seconds to +80 seconds). Each time slice has a step size of 5 seconds.

To answer RQ1, the best features in indicating seizure onset are those ones that give a direct indication for the moment of time of how strong the change in HRV is, like HR_DIFF (differentiation of R-R intervals) or CSI/CSIM (poincaré plot analyzing each R-R interval against the following one) or VLF which were also indicated by feature importance tests.

Using only separate time slices starting at the labeled seizure onset time shows decreasing model performance with each further time slice. The reason is likely that features such as HR_DIFF or CSI/CSIM are directly related to changes in heart rate (variability), which tend to be greatest at seizure onset. This aligns with the seen behavior at using pre-seizure time slices where the peak performance was still only reached with the seizure onset time slice. However, when multiple time slices are incorporated and used for evaluation, a performance decline occurs later after time slice 14 (95 seconds after seizure onset).

However, for answering RQ2, further tests with more reliable data need to be done as our datasets couldn't deliver sufficient information due to a vast amount of missing values for age and gender and even less for height and weight which is why they were skipped in model training. Moreover, additional data like applied treatments were not available at all and even with the sparse data of age and gender, model performance couldn't be improved. Besides these issues, which make it impossible to answer RQ2 at all and require further investigation, there are several more limitations as following.

First of all, data quality might be an overall issue in terms of different recording centers using different recording devices with sensors that have different precision and accuracy leading to additional noise. This might be mitigated by grouping datasets per recording device but would then require the exact same recording environment across different clinics, including the same medic to label the data.

Concerning the experiment of using pre-ictal phase time slices for performance enhancement, it is not clear if the onset timestamps in our data mark the actual beginning of the ictal phase. In case of actually being labeled during the pre-ictal phase due to heart rate changes without strong HRV during the ictal phase, the model performance with its peak at the as seizure onset labeled timestamp is consequential. Otherwise, it is questionable if the medically approved symptom of potential HRV during pre-ictal phase is just not replicated in the data or the detection model needs to be enhanced. Therefore, further tests with clear labeled timestamps (pre-ictal/ictal) are required at this point. Additionally, a third experiment which incorporates combination of multiple, non-consecutive time slices from the pre-ictal as well as the ictal phase might be revealing. This could be implemented in the form of an exhaustive search across all time slices.

And to solidify its efficacy for real-world, daily activity-based applications, ECG recordings from epilepsy patients in non-clinical settings while conducting routine activities or exercising are indispensable. Integrating such data into the model's training process can significantly enhance its robustness and performance for everyday usage.

Finally, the feature set should be refined and retested with different variants using the leading features perceived from the analysis. Although all features rely only on the ECG recordings and can thus always be calculated, too complex models might have a negative impact on model performance.

And while the multifaceted approach to feature importance evaluation, encompassing multiple metrics, provides a robust foundation for indicating the pivotal features of the model, it's also important to note that the interpretation of feature importance can be nuanced, particularly in the context of XGBoost's Gain metric. Variables with binary values, such as "gender", might appear to have lower importance based on frequency-related metrics due to their limited range of values. However, they can exhibit substantial Gain values if they significantly enhance prediction accuracy when utilized in decision tree splits.

While the findings of this study present a very promising approach to seizure detection using gradient boosting algorithms, the listed limitations serve as a starting point for future research to challenge it against other datasets and especially further performance enhancement. Examination of the impact of patient-specific data and test cases with data of real-world activities are significant at this point.

References

Aimaier, G., Qian, K., Zheng, Z., Peng, W., Zhang, Z., Ding, J., and Wang, X. 2022. "Interictal Heart Rate Variability as a Biomarker for Comorbid Depressive Disorders among People with Epilepsy," *Brain Sci* (12:5), p. Article 671.

Behbahani, S., Dabanloo, N. J., Nasrabadi, A. M., and Dourado, A. 2016. "Prediction of Epileptic Seizures Based on Heart Rate Variability," *Technol Health Care* (24:6), pp. 795-810.

Behbahani, S., Jafarnia Dabanloo, N., Motie Nasrabadi, A., Teixeira, C. A., and Dourado, A. 2014. "A New Algorithm for Detection of Epileptic Seizures Based on Hrv Signal," *Journal of Experimental & Theoretical Artificial Intelligence* (26:2), pp. 251-265.

Bernardi, L., Wdowczyk-Szulc, J., Valenti, C., Castoldi, S., Passino, C., Spadacini, G., and Sleight, P. 2000. "Effects of Controlled Breathing, Mental Activity and Mental Stress with or without Verbalization on Heart Rate Variability," *J Am Coll Cardiol* (35:6), pp. 1462-1469.

Billeci, L., Marino, D., Insana, L., Vatti, G., and Varanini, M. 2018. "Patient-Specific Seizure Prediction Based on Heart Rate Variability and Recurrence Quantification Analysis," *PLoS One* (13:9), p. e0204339.

Cogan, D., Birjandtalab, J., Nourani, M., Harvey, J., and Nagaraddi, V. 2017. "Multi-Biosignal Analysis for Epileptic Seizure Monitoring," *Int J Neural Syst* (27:1), p. Article 1650031.

Cygankiewicz, I., and Zareba, W. 2013. "Heart Rate Variability," *Handb Clin Neurol* (117), pp. 379-393.

De Cooman, T., Kjaer, T. W., Van Huffel, S., and Sorensen, H. B. 2018. "Adaptive Heart Rate-Based Epileptic Seizure Detection Using Real-Time User Feedback," *Physiol Meas* (39:1), p. Article 014005.

Devinsky, O. 2004. "Effects of Seizures on Autonomic and Cardiovascular Function," *Epilepsy Curr* (4:2), pp. 43-46.

Eggleston, K. S., Olin, B. D., and Fisher, R. S. 2014. "Ictal Tachycardia: The Head-Heart Connection," *Seizure* (23:7), pp. 496-505.

Evrengul, H., Tanriverdi, H., Dursunoglu, D., Kaftan, A., Kuru, O., Unlu, U., and Kilic, M. 2005. "Time and Frequency Domain Analyses of Heart Rate Variability in Patients with Epilepsy," *Epilepsy Res* (63:2-3), pp. 131-139.

Fujiwara, K., Miyajima, M., Yamakawa, T., Abe, E., Suzuki, Y., Sawada, Y., Kano, M., Maehara, T., Ohta, K., Sasai-Sakuma, T., Sasano, T., Matsuura, M., and Matsushima, E. 2016. "Epileptic Seizure Prediction Based on Multivariate Statistical Process Control of Heart Rate Variability Features," *IEEE Trans Biomed Eng* (63:6), pp. 1321-1332.

Gacek, A., and Pedrycz, W. 2012. *Ecg Signal Processing, Classification and Interpretation*, (1 ed.). Springer London.

Gagliano, L., Assi, E. B., Toffa, D. H., Nguyen, D. K., and Sawan, M. 2020. "Unsupervised Clustering of Hrv Features Reveals Preictal Changes in Human Epilepsy," *Annu Int Conf IEEE Eng Med Biol Soc* (2020), pp. 698-701.

Giannakakis, G., Tsiknakis, M., and Vorgia, P. 2019. "Focal Epileptic Seizures Anticipation Based on Patterns of Heart Rate Variability Parameters," *Comput Methods Programs Biomed* (178), pp. 123-133.

Gibbons, C. H. 2019. "Basics of Autonomic Nervous System Function," *Handb Clin Neurol* (160), pp. 407-418.

Gopinathannair, R., and Olshansky, B. 2015. "Management of Tachycardia," *F1000Prime Rep* (7), p. Article 60.

Halhuber, M. J., Günther, R., and Ciresa, M. 1979. *Ecg an Introductory Course*, (1 ed.). Springer Berlin, Heidelberg.

Hammerle, P., Eick, C., Blum, S., Schlageter, V., Bauer, A., Rizas, K. D., Eken, C., Coslovsky, M., Aeschbacher, S., Krisai, P., Meyre, P., Vesin, J. M., Rodondi, N., Moutzouri, E., Beer, J., Moschovitis, G., Kobza, R., Di Valentino, M., Corino, V. D. A., Laureanti, R., Mainardi, L., Bonati, L. H., Sticherling, C., Conen, D., Osswald, S., Kuhne, M., Zuern, C. S., and Swiss, A. F. S. I. 2020. "Heart Rate Variability Triangular Index as a Predictor of Cardiovascular Mortality in Patients with Atrial Fibrillation," *J Am Heart Assoc* (9:15), p. e016075.

Jahanbekam, A., Baumann, J., Nass, R. D., Bauckhage, C., Hill, H., Elger, C. E., and Surges, R. 2021. "Performance of Ecg-Based Seizure Detection Algorithms Strongly Depends on Training and Test Conditions," *Epilepsia Open* (6:3), pp. 597-606.

Jansen, K., and Lagae, L. 2010. "Cardiac Changes in Epilepsy," *Seizure* (19:8), pp. 455-460.
Jeppesen, J., Beniczky, S., Fuglsang-Frederiksen, A., Sidenius, P., and Jasemian, Y. 2010. "Detection of Epileptic-Seizures by Means of Power Spectrum Analysis of Heart Rate Variability: A Pilot Study," *Technol Health Care* (18:6), pp. 417-426.
Jeppesen, J., Beniczky, S., Johansen, P., Sidenius, P., and Fuglsang-Frederiksen, A. 2014. "Using Lorenz Plot and Cardiac Sympathetic Index of Heart Rate Variability for Detecting Seizures for Patients with Epilepsy," *Annu Int Conf IEEE Eng Med Biol Soc* (2014), pp. 4563-4566.
Jeppesen, J., Beniczky, S., Johansen, P., Sidenius, P., and Fuglsang-Frederiksen, A. 2015. "Detection of Epileptic Seizures with a Modified Heart Rate Variability Algorithm Based on Lorenz Plot," *Seizure* (24), pp. 1-7.
Jeppesen, J., Christensen, J., Johansen, P., and Beniczky, S. 2023. "Personalized Seizure Detection Using Logistic Regression Machine Learning Based on Wearable Ecg-Monitoring Device," *Seizure* (107), pp. 155-161.
Jeppesen, J., Fuglsang-Frederiksen, A., Johansen, P., Christensen, J., Wustenhagen, S., Tankisi, H., Qerama, E., and Beniczky, S. 2020. "Seizure Detection Using Heart Rate Variability: A Prospective Validation Study," *Epilepsia* (61 Suppl 1), pp. 41-46.
Jeppesen, J., Fuglsang-Frederiksen, A., Johansen, P., Christensen, J., Wustenhagen, S., Tankisi, H., Qerama, E., Hess, A., and Beniczky, S. 2019. "Seizure Detection Based on Heart Rate Variability Using a Wearable Electrocardiography Device," *Epilepsia* (60:10), pp. 2105-2113.
Karasmanoglou, A., Antonakakis, M., and Zervakis, M. 2023. "Ecg-Based Semi-Supervised Anomaly Detection for Early Detection and Monitoring of Epileptic Seizures," *Int J Environ Res Public Health* (20:6), p. Article 5000.
Keilson, M. J., Hauser, W. A., and Magrill, J. P. 1989. "Electrocardiographic Changes During Electrographic Seizures," *Arch Neurol* (46:11), pp. 1169-1170.
Massetani, R., Strata, G., Galli, R., Gori, S., Gneri, C., Limbruno, U., Di Santo, D., Mariani, M., and Murri, L. 1997. "Alteration of Cardiac Function in Patients with Temporal Lobe Epilepsy: Different Roles of Eeg-Ecg Monitoring and Spectral Analysis of Rr Variability," *Epilepsia* (38:3), pp. 363-369.
Mazzola, L., and Rheims, S. 2021. "Ictal and Interictal Cardiac Manifestations in Epilepsy. A Review of Their Relation with an Altered Central Control of Autonomic Functions and with the Risk of Sudep," *Front Neurol* (12), p. Article 642645.
McCorry, L. K. 2007. "Physiology of the Autonomic Nervous System," *Am J Pharm Educ* (71:4), p. 78.
Müller, M. 2015. *Fundamentals of Music Processing*, (1 ed.). Springer Cham.
Opherk, C., Coromilas, J., and Hirsch, L. J. 2002. "Heart Rate and Ekg Changes in 102 Seizures: Analysis of Influencing Factors," *Epilepsy Res* (52:2), pp. 117-127.
Őri, Z., Monir, G., Weiss, J., Sayhouni, X., and Singer, D. H. 1992. "Heart Rate Variability," *Cardiology Clinics* (10:3), pp. 499-533.
Persson, H., Ericson, M., and Tomson, T. 2007. "Heart Rate Variability in Patients with Untreated Epilepsy," *Seizure* (16:6), pp. 504-508.
Peters, N., Gatzoulis, M. A., and Vecht, R. 2009. *Ecg Diagnosis in Clinical Practice*, (2 ed.). Springer London.
Petty, B. G. 2020. *Basic Electrocardiography*, (2 ed.). Springer Cham.
Schulze-Bonhage, A., Sales, F., Wagner, K., Teotonio, R., Carius, A., Schelle, A., and Ihle, M. 2010. "Views of Patients with Epilepsy on Seizure Prediction Devices," *Epilepsy Behav* (18:4), pp. 388-396.
Shaffer, F., and Ginsberg, J. P. 2017. "An Overview of Heart Rate Variability Metrics and Norms," *Front Public Health* (5), p. 258.
Smirnov, Y., Popov, A., Panichev, O., Karplyuk, Y., and Kharytonov, V. 2017. "Epileptic Seizure Prediction Based on Singular Value Decomposition of Heart Rate Variability Features," *Signal Processing Symposium (SPSympo)*, pp. 1-4.
Stroobandt, R. X., Barold, S. S., and Sinnaeve, A. F. 2015. *Ecg from Basics to Essentials*, (1 ed.). John Wiley & Sons, Ltd.
Van de Vel, A., Cuppens, K., Bonroy, B., Milosevic, M., Jansen, K., Van Huffel, S., Vanrumste, B., Cras, P., Lagae, L., and Ceulemans, B. 2016. "Non-Eeg Seizure Detection Systems and Potential Sudep Prevention: State of the Art: Review and Update," *Seizure* (41), pp. 141-153.
van Westrhenen, A., De Cooman, T., Lazeron, R. H. C., Van Huffel, S., and Thijs, R. D. 2019. "Ictal Autonomic Changes as a Tool for Seizure Detection: A Systematic Review," *Clin Auton Res* (29:2), pp. 161-181.

Vandecasteele, K., De Cooman, T., Gu, Y., Cleeren, E., Claes, K., Paesschen, W. V., Huffel, S. V., and Hunyadi, B. 2017. "Automated Epileptic Seizure Detection Based on Wearable Ecg and Ppg in a Hospital Environment," *Sensors (Basel)* (17:10), p. Article 2338.

Wannamaker, B. B. 1985. "Autonomic Nervous System and Epilepsy," *Epilepsia* (26 Suppl 1), pp. 31-39.

Wirth, R., and Hipp, J. 2000. "Crisp-Dm: Towards a Standard Process Model for Data Mining," *Proceedings of the 4th international conference on the practical applications of knowledge discovery and data mining* (1), pp. 29-39.

Yamakawa, T., Miyajima, M., Fujiwara, K., Kano, M., Suzuki, Y., Watanabe, Y., Watanabe, S., Hoshida, T., Inaji, M., and Maehara, T. 2020. "Wearable Epileptic Seizure Prediction System with Machine-Learning-Based Anomaly Detection of Heart Rate Variability," *Sensors (Basel)* (20:14), p. Article 3987.

Zambrana-Vinaroz, D., Vicente-Samper, J. M., Manrique-Cordoba, J., and Sabater-Navarro, J. M. 2022. "Wearable Epileptic Seizure Prediction System Based on Machine Learning Techniques Using Ecg, Ppg and Eeg Signals," *Sensors (Basel)* (22:23), p. Article 9372.