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CZECH TECHNICAL UNIVERSITY IN PRAGUE

Faculty of Electrical Engineering

Department of Circuit Theory

Bachelor's thesis

Long-term evolution of seizure characteristics in a mouse model of epilepsy

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May 24, 2024

Supervisor: Ing. Jan Kudláček, Ph.D.

BACHELOR‘S THESIS ASSIGNMENT

I. Personal and study details

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Faculty / Institute: **Faculty of Electrical Engineering**

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Study program: **Medical Electronics and Bioinformatics**

II. Bachelor’s thesis details

Bachelor’s thesis title in English:

Long-term evolution of seizure characteristics in a mouse model of epilepsy

Bachelor’s thesis title in Czech:

Dlouhodobý vývoj charakteristiky záchvatů v myším modelu epilepsie

Guidelines:

Epilepsy is a serious chronic neurological disorder affecting 0.5 - 1 % of population in developed countries. In only 70% of patients current pharmacological treatments are successful. Moreover, they often have significant adverse effects. Improvement could be achieved through chronotherapy, i.e. application of the drugs at the times when they are most effective and have least adverse effects [1]. This requires detailed knowledge of the natural course of the disease. Recently, a lot of knowledge has been gained about the spontaneous long-term fluctuations in the probability of seizure occurrence [2]. There have been, however, only few studies of the natural evolution of the characteristics of the seizures [3, 4, 5]. The student will analyze EEG characteristics of hundreds of seizures recorded in laboratory mice. The results will be highly valuable for the understanding of the natural course of the disease. Moreover, the developed algorithms can be used in the assessment of novel therapies. The tasks for the student are:
1) For each seizure, compute characteristics of the EEG signal in 1-s bins. The characteristics should include variance and first spectral moment. More characteristics are welcome.
2) The characteristics will create a trajectory of the seizure in an N-dimensional space.
3) Use dynamic time warping technique to evaluate the similarity between the trajectories.
4) Test the hypothesis that seizures which occurred closer to each other in time have more similar trajectory.

Bibliography / sources:

[1] Karoly et al.: Cycles in epilepsy. Nat Rev Neurol 2021. doi: 10.1038/s41582-021-00464-1
[2] Leguia et al.: Seizure Cycles in Focal Epilepsy. JAMA Neurol 2021. doi: 10.1001/jamaneurol.2020.5370
[3] Kudlacek et al.: Long-term seizure dynamics are determined by the nature of seizures and the mutual interactions between them. Neurobiol Dis 2021. doi: 10.1016/j.nbd.2021.105347
[4] Schroeder et al.: Seizure pathways change on circadian and slower timescales in individual patients with focal epilepsy. PNAS 2020. doi: 10.1073/pnas.1922084117
[5] Crisp et al.: Quantifying epileptogenesis in rats with spontaneous and responsive brain state dynamics. Brain Commun 2020. doi: 10.1093/braincomms/fcaa048

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Supervisor’s signature	Head of department’s signature	Dean’s signature

III. Assignment receipt

The student acknowledges that the bachelor's thesis is an individual work. The student must produce his thesis without the assistance of others, with the exception of provided consultations. Within the bachelor's thesis, the author must state the names of consultants and include a list of references.

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Date of assignment receipt

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Declaration

I declare that the presented work was developed independently and that I have listed all sources of the information used within it in accordance with the methodical instructions for observing the ethiclal principles in the preparation of university theses.

Prague, May 24, 2024

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Richard Köplinger

Acknowledgement

Completing this thesis marks both an end and a beginning in my academic journey. I am profoundly grateful for the support and inspiration I have received, which fuel my pursuit of further knowledge as I transition into my master's studies.

I extend my deepest thanks to my thesis advisor, Ing. Jan Kudláček, Ph.D., whose expertise and insightful guidance were instrumental in shaping this research. Your unwavering patience and dedication has not only helped refine my work but has also prepared me for the challenges ahead in my continued education.

A heartfelt thank you to my family, especially my mother, for her constant encouragement and belief in my capabilities. Your support remains my anchor.

To my friends, thank you for your support and for keeping spirits high during times of stress.

Last but not least, I appreciate everyone who contributed to my journey thus far, knowing that this is not the end but an exciting continuation. I am eager to see what the future holds in my academic career, armed with the knowledge and connections from my bachelor's studies.

Abstract

Epilepsy is a complex neurological disorder characterized by spontaneous recurrent seizures, affecting millions globally. This thesis investigates the long-term evolution of seizure characteristics in a mouse model of epilepsy, aiming to enhance the understanding of seizure dynamics which could inform future treatment strategies. Using intracranial electroencephalogram recordings from laboratory mice, we quantitatively analysed hundreds of seizures by computing signal variances and the main frequencies within defined time bins. The variance and the main frequency then created the a 2-dimensional space in which the unwinding seizure created a pathway. Finally, the pathways of all the seizures were analysed by computing their pair-wise similarity using the dynamic time warping.

Our analysis revealed significant variability in seizure characteristics both within and between subjects, underscoring the complexity of seizure dynamics. The study tested the hypothesis that seizures occurring closer in time are more similar, which was confirmed in 6 out of 11 mice. This variability highlights the need for personalized approaches to epilepsy treatment based on individual seizure dynamics.

The findings suggest that temporal patterns of seizure activity are crucial for understanding the natural progression of epilepsy and could lead to more targeted and effective treatments. This research contributes to the growing field of personalized medicine in epilepsy, emphasizing the need for individualized treatment plans based on detailed, longitudinal seizure data.

Keywords: epilepsy, seizure dynamics, temporal patterns, computational analysis, mouse model, personalized medicine, seizure characteristics, intracranial electroencephalogram (iEEG), dynamic time warping (DTW)

Abstrakt

Epilepsie je komplexní neurologická porucha charakterizovaná spontánními opakujícími se záchvaty, které postihují miliony lidí po celém světě. Tato práce zkoumá dlouhodobý vývoj charakteristik záchvatů u myšího modelu epilepsie s cílem zlepšit porozumění dynamice záchvatů, které by mohly být podkladem budoucích léčebných strategií. Pomocí záznamů intrakraniálního elektroencefalogramu z laboratorních myší jsme kvantitativně analyzovali stovky záchvatů výpočtem rozptylů signálů a hlavních frekvencí v definovaných časových intervalech. Rozptyl a hlavní frekvence pak vytvořily dvourozměrný prostor, v němž odvíjející se záchvat vytvořil trajektorii. Nakonec byly analyzovány trajektorie všech záchvatů výpočtem jejich párové podobnosti pomocí metody dynamic time warpingu.

Naše analýza odhalila významnou variabilitu v charakteristikách záchvatů jak v rámci jednoho subjektu, tak mezi subjekty, což podtrhuje složitost dynamiky záchvatů. Studie testovala hypotézu, že záchvaty vyskytující se blíže v čase jsou si podobnější, což se potvrdilo u 6 z 11 myší. Tato variabilita zdůrazňuje potřebu personalizovaných přístupů k léčbě epilepsie založené na individuální dynamice záchvatů.

Zjištění naznačují, že časové vzorce aktivity záchvatů jsou zásadní pro pochopení přirozeného vývoje epilepsie a mohly by vést k cílenější a účinnější léčbě. Tento výzkum přispívá k rozvíjející se oblasti personalizované medicíny v oblasti epilepsie a zdůrazňuje potřebu individualizovaných léčebných plánů založených na podrobných longitudinálních údajích o záchvatech.

Klíčová slova: epilepsie, dynamika záchvatů, časové vzorce, výpočetní analýza, myší model, personalizovaná medicína, charakteristiky záchvatů, intrakraniální elektroencefalogram (iEEG), dynamické borcení času (DTW)

Překlad názvu: Dlouhodobý vývoj charakteristiky záchvatů v myším modelu epilepsie

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List of Abbreviations

Abbreviation	Meaning
EEG	Electroencephalogram
iEEG	Intracranial electroencephalogram
ISI	Inter-seizure intervals
NMF	Non-negative matrix factorization
ACF	Autocorrelation function
DTW	Dynamic Time Warping
OSEL	Open Signal Explorer and Labeller

Chapter 1
Introduction

1.1 Historical context and current impact of epilepsy

Epilepsy is a serious neurological disorder affecting around 50 million people worldwide. This makes epilepsy the fourth most common brain condition in the world. People recognized this illness as early as 4000 BCE [1]. For many centuries, epilepsy was known as the sacred disease with divine or demonic origin and curable solely by rituals and magical instruments. Only in 400 BCE the Hippocratic treatise, entitled "On the Sacred Disease", was published, criticising the magical and superstitious conceptions and modes of epilepsy. Its author is credited to be the first one to attempt a rational explanation of a disease [2]. Even though thousands of years from this time have passed, there is a continuing social stigma, fear and discrimination affecting the lives of epileptic patients and their families. According to the World Health Organisation, many low-income or middle-income countries withhold rights from patients suffering from epilepsy, such as the right to education or accessing restaurants, theatres and other recreational or public facilities. These oppressions are making people that need help isolated and frightened to seek professional treatment [1]. This is one of the many reasons why much more research and education of the general public in this field is needed.

1.2 Definition and pathophysiology of epilepsy

According to the International League Against Epilepsy, epilepsy is defined as follows: *"Epilepsy is a disease of the brain defined by any of the following conditions*

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*

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years." [3]

Individuals overcoming status epilepticus or who have only febrile, neonatal or acute symptomatic seizures caused by for example intoxication, substance abuse or other illnesses are not considered epileptic patients [4]. From the pathophysiological point of view, the slow process changing non-epileptic brain to epileptic with the ability of generating seizures is called epileptogenesis. Seizure is a product of imbalance between inhibitory and excitatory activity inside a neural network. This imbalance causes the neural network to be prone to operate in an excessive, hypersynchronous, oscillatory way. When this state is maintained for a longer period, it interferes with normal neuronal processing and can interject other neuronal networks [5].

1.3 Challenges in epilepsy treatment and the need for advanced research

Despite advances in medical science, the treatment of epilepsy remains a significant challenge. Currently, pharmacological interventions successfully control seizures in only about 70 % of patients with epilepsy [6], and many experience severe side effects. These limitations highlight the urgent need for more profound insights into the natural course of epilepsy and the mechanisms underlying seizure generation. Such understanding is crucial for developing a treatment tailored not only to the given patient but also to his or her current state.

To improve treatment strategies, it is imperative to explore the non-random nature of seizure occurrences and their clustering, which deviates from what would be expected in a purely random, Poisson distribution. This exploration not only aids in understanding the complex interactions within the brain that lead to seizures but also in developing predictive models that can forecast seizure events with greater accuracy [7].

1.4 Seizure clustering and predictability

In many patients and animal models of epilepsy, seizures are not Poissonian but occur clustered in patterns that can be statistically analysed [8]. Utilizing a tetanus toxin model of temporal lobe epilepsy, their analysis shows that seizures within clusters are distributed in a non-Poissonian manner. The intervals between seizures (inter-seizure intervals, ISI) within a cluster progressively increase, suggesting dynamics where initial non-convulsive seizures increase the likelihood of subsequent convulsive seizures. These convulsive seizures then extend the ISI, contributing to the termination of the seizure cluster. This pattern indicates a 'seizures-beget-seizures' dynamics and suggests that the clustering of seizures is influenced by complex intra-brain interactions and possibly by the reorganization of brain networks.

Such insights underscore the potential of personalized medicine and chronotherapy principles, where understanding individual seizure patterns could lead to more effective, timed interventions that align with the natural clustering of seizures in a patient. By administering medication at times when they are most effective and cause the least side effects, scientists and clinicians could greatly improve patient outcomes [9] [10]. However, the challenge lies in the inherent heterogeneity of epilepsy across patients. This variability underscores the need for developing new biomarkers for seizure progression – measurable indicators of biological processes or disease states that can serve as targets for diagnostic, prognostic, and therapeutic interventions. The development of these biomarkers could crucially enhance our ability to track and forecast disease progression, potentially leading to breakthroughs in the management of epilepsy [7].

1.5 Personalized medicine in epilepsy

Seizure progression is a process by which a partial seizure spreads within a brain. The gradual shifts in underlying physiological mechanisms can be indicated by a trajectory, i.e. path, through the parameter space of a neural mass model. This characterizes the dynamics of EEG activity during epileptic seizures [11]. However, the paths of seizures through the space of possible network dynamics varies between patients with epilepsy. This variability of within-patient evolutions of seizures suggest

that approaches of personalized medicine may be needed [12]. Personalized medicine aims to tailor medical treatments to individual patients based on their genetic and genomic data, physiology and disease manifestations.

1.6 Review of seizure pathways in focal epilepsy

In the study conducted by Schroeder et al. [12], the authors examine the temporal variability of seizure pathways among patients with focal epilepsy. This work is foundational in illustrating the complexity of seizure dynamics, which is characterized by changes not only on a circadian scale but also over longer periods. This section of the thesis reviews their methodologies and findings, offering a contextual basis for the present study focused on similar phenomena in mouse models.

1.6.1 Methodological overview

Schroeder et al. utilized intracranial electroencephalography (iEEG) data collected from multiple patients at several medical institutions. The analysis centered around dynamic time warping (DTW) and non-negative matrix factorization (NMF), which facilitated the investigation of seizure temporal patterns and network dynamics. Dynamic time warping was particularly crucial for aligning seizures that varied in timing and manifestation within the patients, thereby enabling a comparative analysis of their network evolution characteristics. This approach underscored the variability within and across individual seizure episodes, suggesting a complex interplay between neuronal networks over time.

1.6.2 Findings and their implications

The study revealed significant intra-patient variability in seizure pathways, which were influenced by circadian rhythms and slower evolving temporal patterns. One of the important discoveries was the lack of a clear relationship between seizure variability and conventional clinical parameters, such as the anatomical onset of seizures or specific pathological features. This insight challenges the traditional paradigms of epilepsy treatment and underscores the necessity for personalized therapeutic strategies that consider the temporal dynamics of seizure activities.

Moreover, the study highlighted that the methodologies employed, such as DTW, could detect nuanced changes in the seizure pathways that might not be apparent through conventional analysis techniques. The implications of these findings are profound, suggesting that seizure management could benefit significantly from considering the temporal patterns in seizure activity, which may lead to more targeted and effective intervention strategies.

1.6.3 Relevance to present study

The methodologies and findings from Schroeder et al. provide a critical framework for this thesis, which aims to explore similar patterns in a mouse model of epilepsy. By adapting some of their analytical techniques, this study seeks to uncover whether the temporal variability observed in human epilepsy is similarly present in mice. Such comparative analysis could not only validate the findings

from Schroeder et al. but also expand on them by exploring the potential biological underpinnings that govern these dynamics in a controlled experimental setting.

In conclusion, the investigation into the temporal variability of seizure pathways by Schroeder et al. is a seminal work that contributes significantly to the field of epilepsy research. By demonstrating that seizure pathways are not static but vary according to circadian and slower timescales, they provide a new lens through which epilepsy can be understood and treated. The current thesis builds on this foundation, aiming to further dissect these phenomena within the context of mouse models of epilepsy, thereby contributing to the broader understanding of seizure dynamics across species. This investigation not only aims to replicate foundational human studies within a new model but also to identify and characterize mechanisms that could eventually inform more effective interventions.

1.7 Research focus and objectives

The objective of this study is to analyse the long-term evolution of seizure characteristics in a mouse model of epilepsy through extensive iEEG recordings. The primary goal is to characterize seizure dynamics by computing signal variance and the main frequency within bins of a signal. These metrics will be used to construct trajectories in an N-dimensional space, capturing the multifaceted progression of seizures. To assess similarities between these trajectories, Dynamic Time Warping (DTW) will be employed, which is efficient in comparing sequences that may vary over time. This study will test the hypothesis that seizures occurring closer in time exhibit more similar trajectories, using statistical methods to analyse the correlation between temporal proximity and trajectory similarity. The use of DTW in this research not only highlights the dynamic nature of seizure activity but also underscores the potential for sophisticated computational tools to reveal subtle patterns in biomedical data that might otherwise remain obscured. These efforts could pave the way for future studies focused on predicting the characteristics of future seizures and tailoring interventions more effectively.

Chapter 2
Materials and methods

2.1 Animal model of epilepsy and EEG recordings

In this study, we used a mouse model of epilepsy to explore the dynamics of seizures. iEEG recordings were collected from epileptic mice, utilizing four epidural electrodes implanted over the frontal and parietal cortices of their brain to capture neural activity. The recordings were conducted at a sample rate of 250 Hz. All analyses were conducted in MATLAB programming environment.

2.2 Seizure extraction

To characterize the long-term evolution of seizure characteristics, seizures were first extracted from the raw EEG recordings. Seizure labels, indicating the start and end times, were created by a specialist in the field after a visual inspection of the iEEG recordings. I extracted also 10 seconds pre- and post-seizure, therefore, during a segmentation, the first 9 windows of the seizure data were padded by the pre-seizure data and the last 9 windows were padded by the post-seizure data. In comparison with zero-padding, this reflects also seizure dynamics before and after a seizure in the analysis.

2.3 Computation of seizure parameters

We adopted and substantially modified the analysis approach of Schroeder et al. [12]. We segmented the data in 10 s bins with 90% overlap and in each segment computed the following characteristics:

1. **Power:**

$$P = \frac{1}{N}\sum_{k=1}^{N} s[k]^2 \tag{1}$$

   where N is the total number of samples in a segment and $s[k]$ is the value of the EEG signal in sample k.
2. **Variance:**

$$Var(s) = \sigma^2 = \frac{1}{N}\sum_{k=1}^{N}(s[k] - \mu)^2 \tag{2}$$

   where μ is the average value

$$\mu = \frac{1}{N}\sum_{k=1}^{N} s[k] \tag{3}$$

3. **Autocorrelation function (ACF) Lag-1:**

$$R[m] = \frac{\sum_1^{N-m}(s[k]-\mu)(s[k+m]-\mu)}{\sigma^2} \tag{4}$$

where m is the lag in samples, μ is calculated as in 3 and σ^2 was defined in 2. ACF Lag-1 corresponds to the value $R[m=1]$.

4. **Main frequency:** Derived from the second highest peak of the ACF, the main frequency highlights the dominant rhythmic activity during seizures, providing a focal point for frequency-based analysis in the DTW process. In case there is no second peak present, the value of main frequency is set to 0. We are aware that in the thesis assignment is mentioned the first spectral moment. However, we decided for the main frequency due to the greater robustness of the ACF method to potential random noise.
5. **Similarity index:** This index quantifies the degree of similarity between the semiperiodic elements, providing a measure of the resemblance between EEG patterns. Mathematically, it is the normalized value of ACF in the point corresponding to the main frequency, i.e. the height of the second peak.

2.4 Seizure pathways

To understand the dynamic nature of seizures, I constructed seizure pathways using the calculated parameters from the EEG data. For simplicity and easier visualisation, we used only variance and the main frequency, but in theory, any number of characteristics could be used. To smooth the curve, first I applied a moving average filter with a sliding window of 5 samples on the characteristics. Then I generated the pathways by plotting the variance of the EEG signal against its main frequency. The visual trajectories were color-coded based on the normalized time index, providing a clear depiction of how the seizures evolved from the onset to the termination.

The pathways provide a foundational tool for subsequent analyses, including the application of DTW to assess similarities across seizures, which is described in the following section.

2.5 Analysis of seizure pathways

2.5.1 Dynamic time warping and dissimilarity matrix

DTW was applied to analyse the temporal alignment of seizure events within the same subject. I used MATLAB's dtw() function to implement this analysis. Instead of the classical Euclidian distance I chose the L1 distance metric, also known as the Manhattan distance, due to its effectiveness in linearly representing differences between sequences:

$$DTW_{distance} = \sum |x_i - y_i| \tag{5}$$

where x and y are the time-aligned sequences being compared.

The results were compiled into a dissimilarity matrix for each subject, visually encoding the degree of similarity between seizures, with each element of the matrix representing the normalized DTW distance between seizure pairs:

$$NormalizedDistance = \frac{Distance - MinDistance}{MaxDistance - MinDistance} \tag{6}$$

2.5.2 Temporal distance matrix

To enhance the interpretability of the data, I employed a dual-matrix visualization approach. The first matrix visualizes seizure dissimilarities, as previously described, while the second matrix displays the pairwise temporal distances using the same color-coded scale. This visualization technique allows for an immediate visual comparison between the similarity in seizure characteristics and their temporal proximity.

2.5.3 Pearson's correlation

To quantify the relationship between seizure dissimilarity and temporal proximity, I plotted seizure dissimilarity against temporal distances. Using this scatter plot, I calculated Pearson's correlation coefficient to assess the degree of linear correlation between these two features. This statistical measure provides insights into whether seizures that occur closer in time are more similar in their characteristics, which could suggest underlying patterns in seizure genesis or propagation.

2.6 Supplementary material

All developed scripts used for this thesis are attached.

Chapter 3
Results

3.1 Analysis of seizure characteristics and visualization

In the first step, I computed various characteristics of seizures from EEG data, including variance and the main frequency, to understand their behaviour over time. These parameters were critical in characterizing the dynamic nature of seizures within our data set. For detailed visualizations of EEG alongside computed characteristics, I used the Open Signal Explorer and Labeller (OSEL) – interactive MATLAB based viewer written by my supervisor. Figure 1 below is a screenshot from the OSEL interface, showcasing the EEG data and the associated seizure characteristics. After a visual inspection of all seizures in OSEL, I excluded seizures containing artefacts from the analyses.

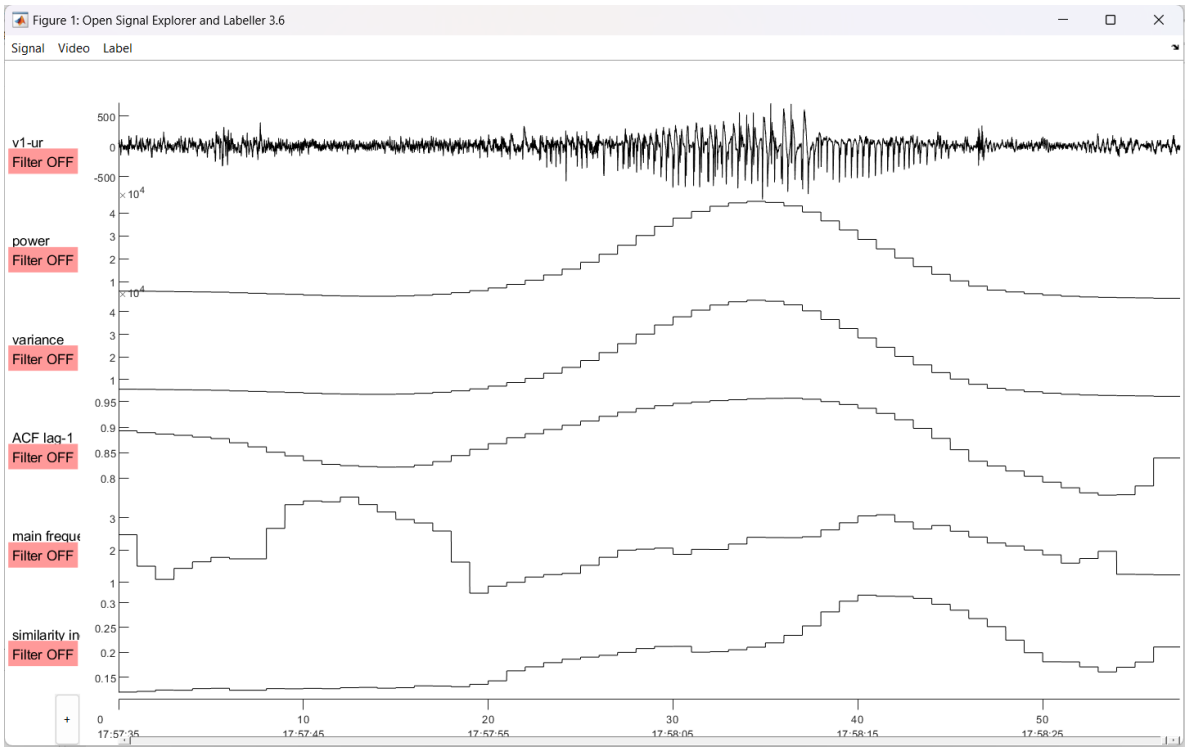


Figure 1: Representative seizure profile depicting EEG signal alongside computed parameters. Channels from top to bottom are: iEEG, power, variance, ACF lag-1, main frequency and similarity index. Visualization was done by utilizing the OSEL software.

3.2 Seizure pathways and dynamic time warping analysis

The core part of this study was to utilize the afore mentioned characteristics to visualize and analyse seizure pathways by employing DTW. By mapping these pathways, we can better understand

the patterns of the dynamic progression of seizures. The following subsections will detail the analysis for each test subject, supported by figures that illustrate the pathways and highlight the results from the analyses. In total, 394 seizures from 11 mice were analysed.

The figures are organised uniformly in the following matter:

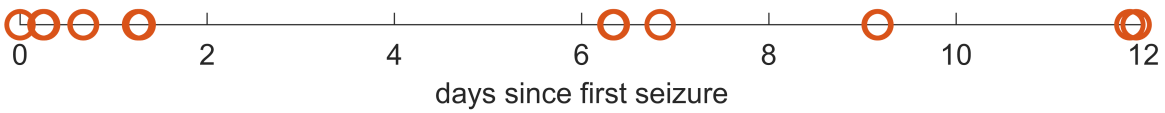
(a) The linear profile shows the time of each seizure (orange circles) relative to the first seizure.
(b) The seizure pathway plot reveals all trajectories of seizure activity through the variance vs. main frequency space.
(c) The dissimilarity matrix showcases the variation in seizure characteristics across different events, with warmer colors (i.e. red) indicating greater dissimilarity.
(d) The temporal distance matrix quantifies the amount of time between each pair of seizures, in days, with colder colors (i.e. blue) indicating low distance.
(e) Comparison of seizure dissimilarities and temporal distances plot. Above the plot is a Pearson's correlation coefficient ρ between the two features and a p-value of this correlation.

3.2.1 General patterns observed in most subjects

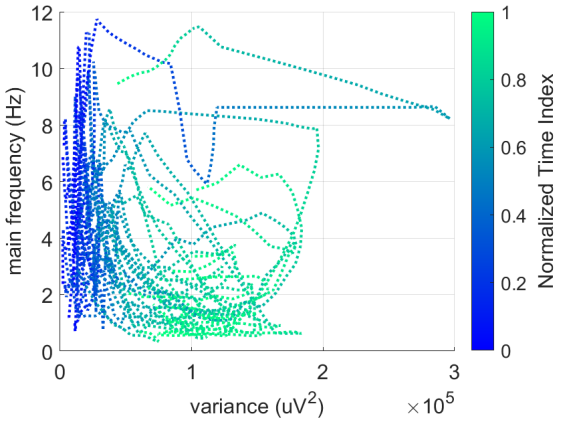
The general trend observed across the dataset highlighted that seizures typically initiated at low variance levels with frequencies that varied widely, quickly escalating in variance before tapering off as the seizures concluded. This pattern was consistently observed, with high frequencies generally declining towards the end of a seizure, often coupled with an increase in variance, suggesting a phase of heightened neural activity followed by a return to baseline states.

3.2.2 Results for subject jc20181211_1

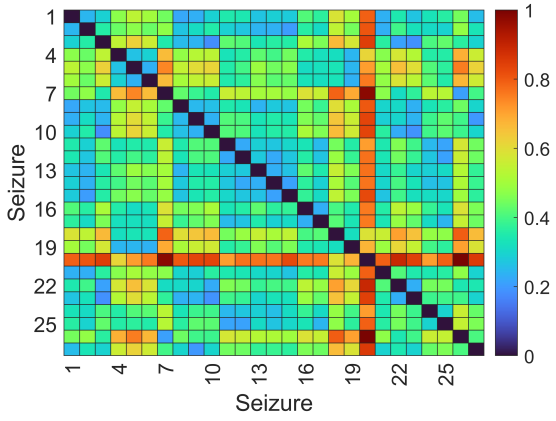
Analysis of this subject displayed a pattern of early clustered seizures post-onset with no significant correlation between temporal proximity and seizure similarity, suggesting independent seizure dynamics (Pearson's $\rho = 0.05, p = 0.17$).



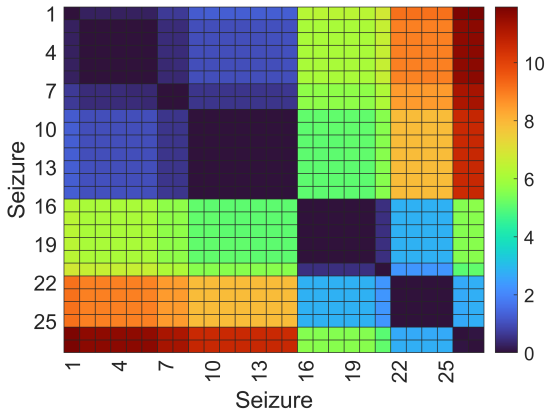
(a) The linear profile of subject's seizures.



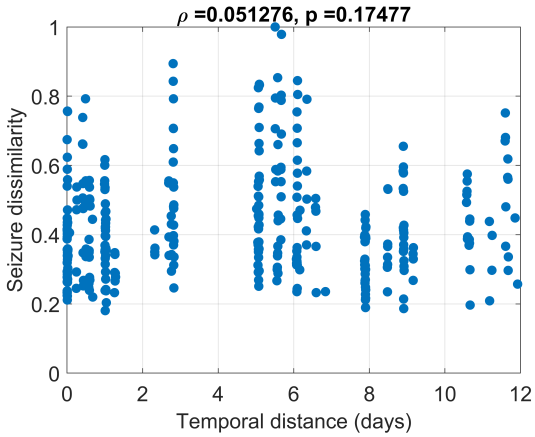
(b) Seizure pathways.



(c) Dissimilarity matrix.



(d) Temporal distance matrix.

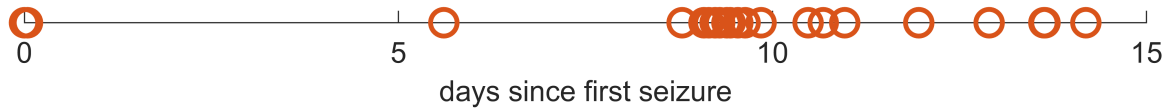


(e) Seizure dissimilarity vs. temporal distance.

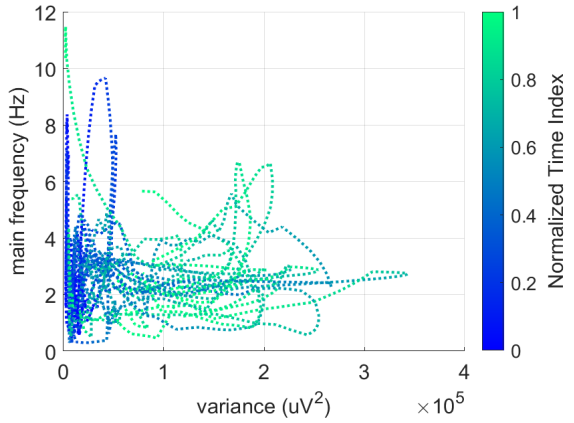
Figure 2: Analysis results for subject jc20181211_1.

3.2.3 Results for subject jc20181218_1

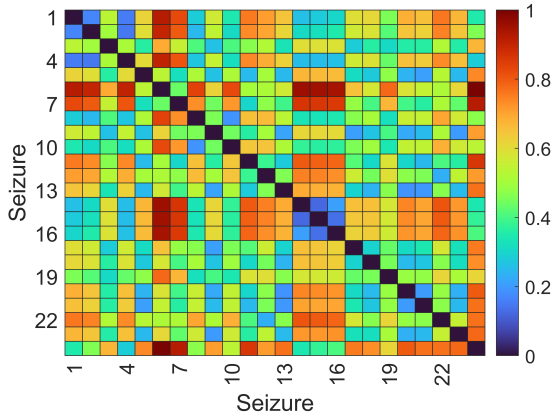
This subject showed a pattern where seizure characteristics were less predictable and did not correlate significantly with the timing of seizures, indicating unique seizure dynamics unrelated to temporal distribution (Pearson's $\rho = 0.03, p = 0.52$). There are two large clusters noticeable. One is around day 10 post-onset and second one is not very well visible in the linear profile due to its high density, but is around day 14.



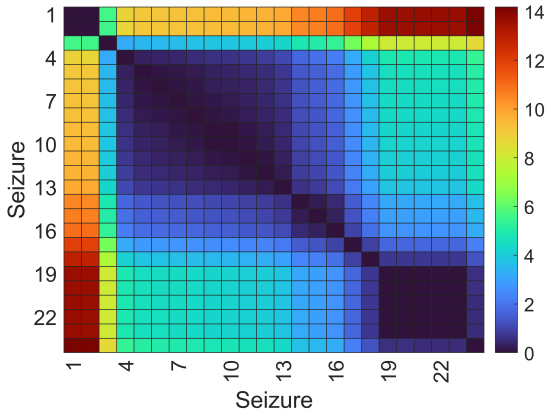
(a) The linear profile of subject's seizures.



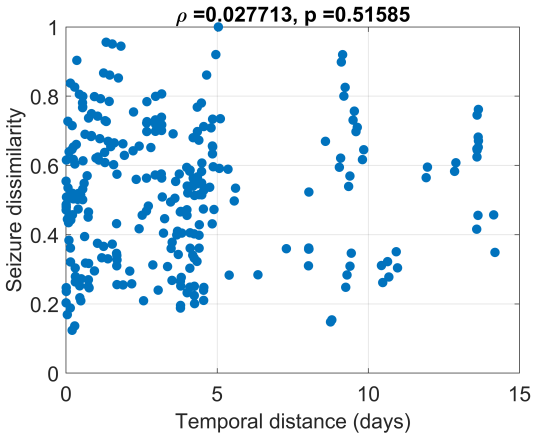
(b) Seizure pathways.



(c) Dissimilarity matrix.



(d) Temporal distance matrix.

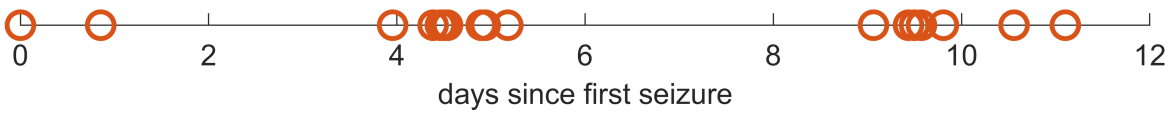


(e) Seizure dissimilarity vs. temporal distance.

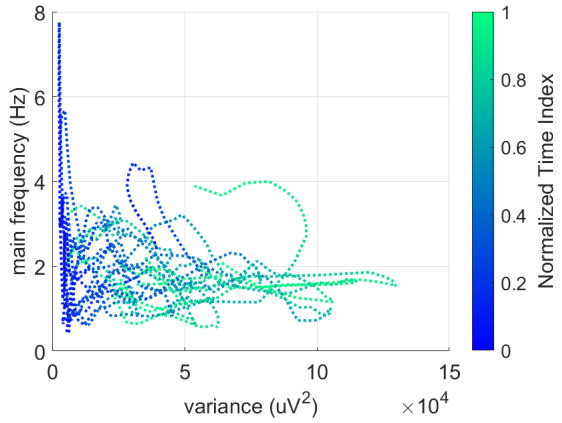
Figure 3: Analysis results for subject jc20181218_1.

3.2.4 Results for subject jc20181219_2

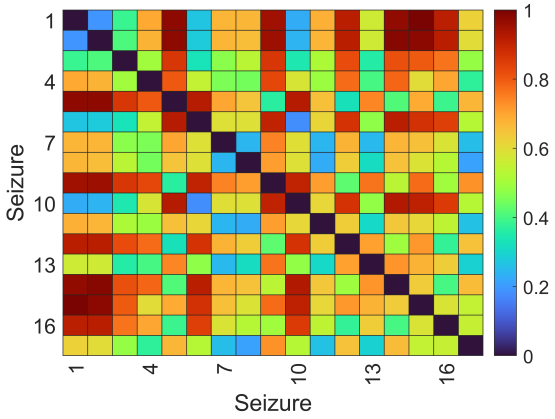
The analysis exhibited two noticeable clusters of seizures around days 5 and 10 post-onset. Although the seizures within these clusters appeared quite dissimilar in the dissimilarity matrix, indicating varied seizure dynamics, there was still a statistically significant positive correlation between the timing and the characteristics of these seizures (Pearson's $\rho = 0.21, p = 0.0006$).



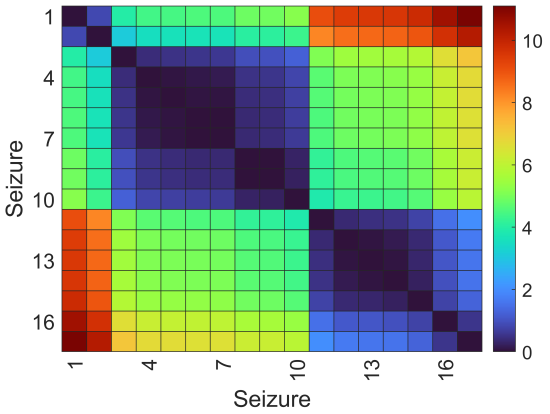
(a) The linear profile of subject's seizures.



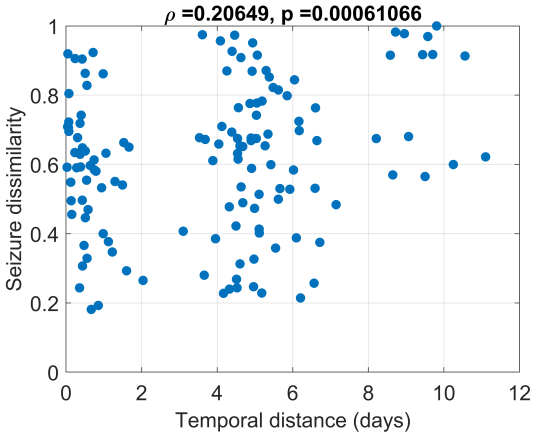
(b) Seizure pathways.



(c) Dissimilarity matrix.



(d) Temporal distance matrix.

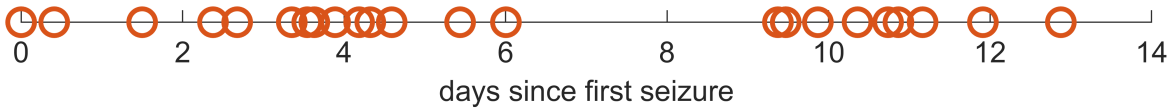


(e) Seizure dissimilarity vs. temporal distance.

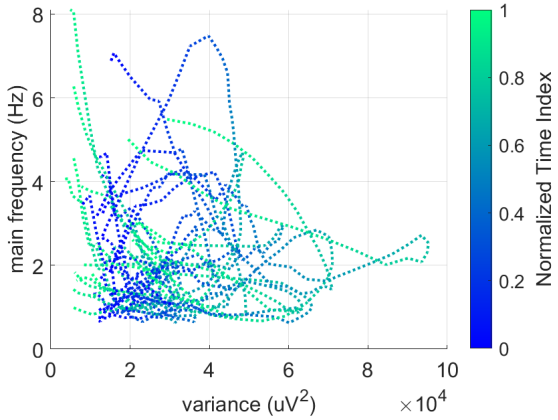
Figure 4: Analysis results for subject jc20181219_2.

3.2.5 Results for subject jc20181219_4

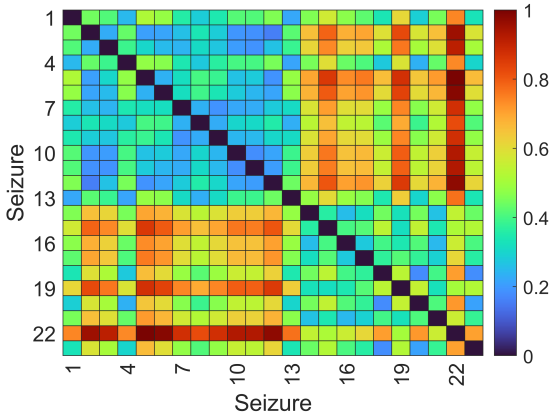
Exhibited a strong correlation between the timing and characteristics of seizures, suggesting a stable seizure pattern (Pearson's $\rho = 0.55, p = 7.3 \cdot 10^{-41}$).



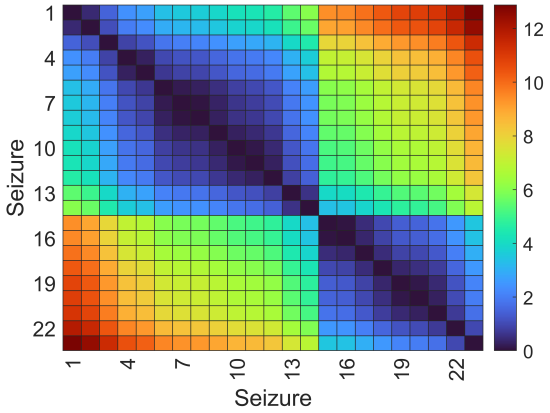
(a) The linear profile of subject's seizures.



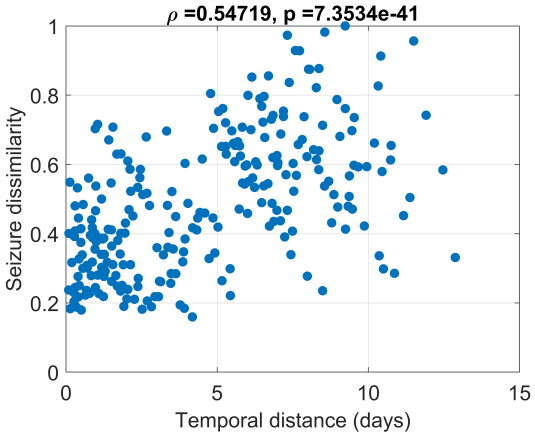
(b) Seizure pathways.



(c) Dissimilarity matrix.



(d) Temporal distance matrix.

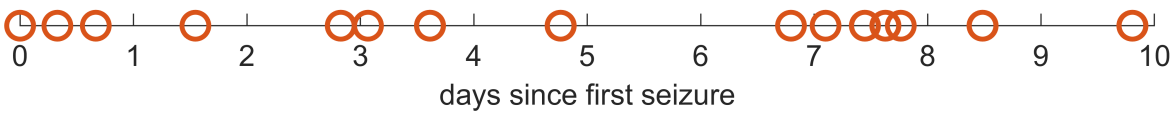


(e) Seizure dissimilarity vs. temporal distance.

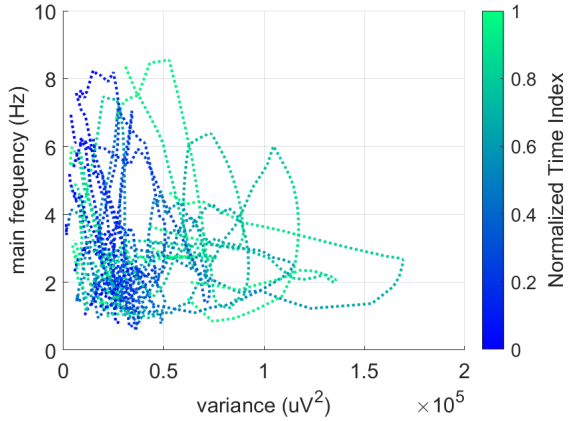
Figure 5: Analysis results for subject jc20181219_4.

3.2.6 Results for subject jc20190103_3

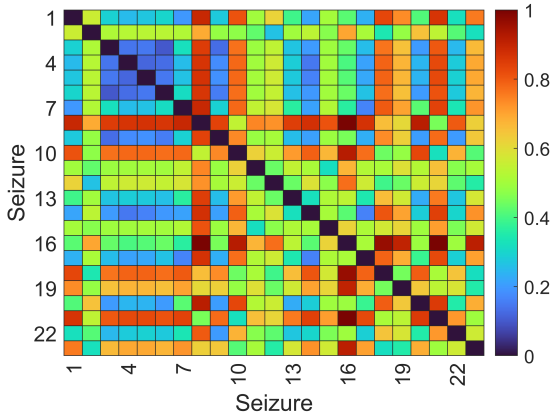
This subject has an interesting correlation between dissimilarity and distance (Pearson's $\rho = -0.08, p = 0.07$), because the correlation is slightly negative and almost significant. Unfortunately, there does not appear to be an obvious reason for this anomaly.



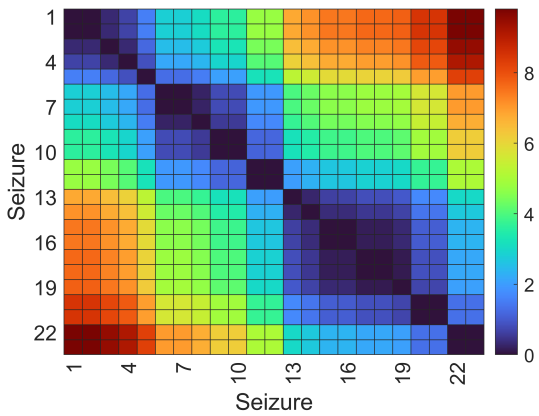
(a) The linear profile of subject's seizures.



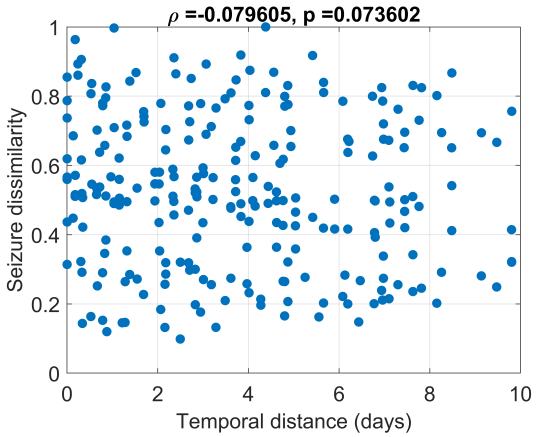
(b) Seizure pathways.



(c) Dissimilarity matrix.



(d) Temporal distance matrix.



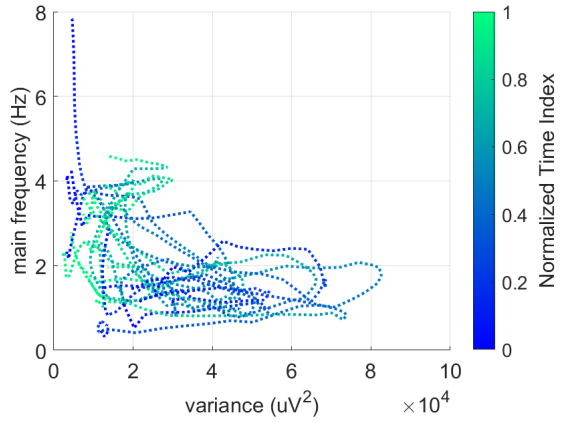
(e) Seizure dissimilarity vs. temporal distance.

Figure 6: Analysis results for subject jc20190103_3.

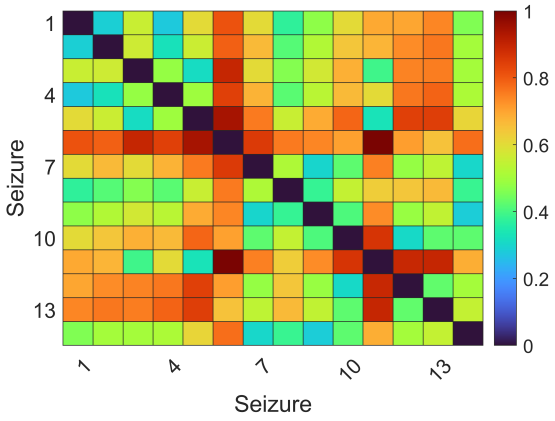
3.2.7 Results for subject jc20190313_2

Despite the temporal clustering of seizures, there was no significant correlation between the timing and similarity of these seizures (Pearson's $\rho = -0.01, p = 0.84$), indicating that seizures closely spaced in time can still exhibit diverse characteristics.

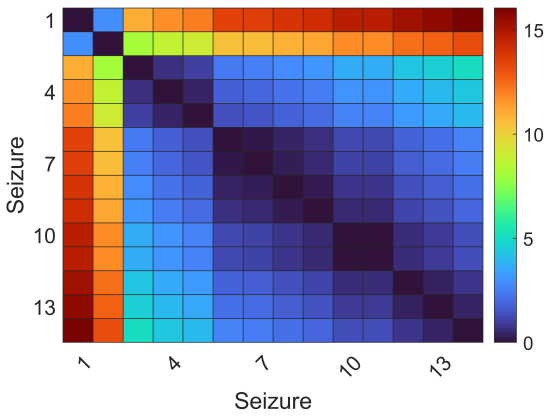
(a) The linear profile of subject's seizures.



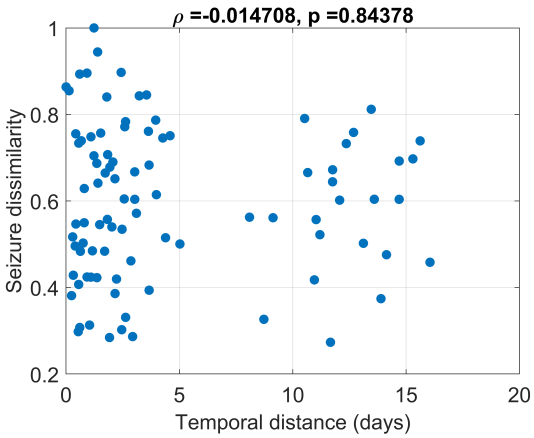
(b) Seizure pathways.



(c) Dissimilarity matrix.



(d) Temporal distance matrix.

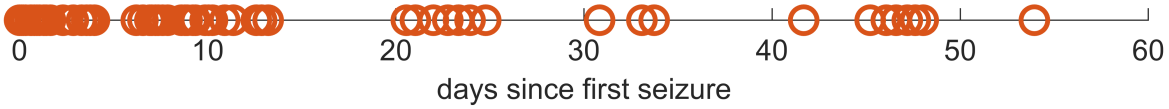


(e) Seizure dissimilarity vs. temporal distance.

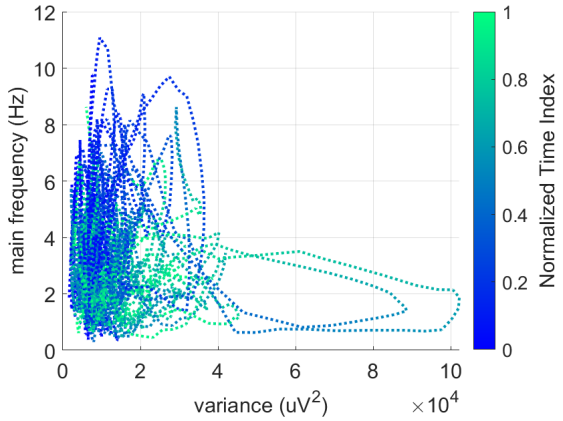
Figure 7: Analysis results for subject jc20190313_2.

3.2.8 Results for subject jc20190313_3

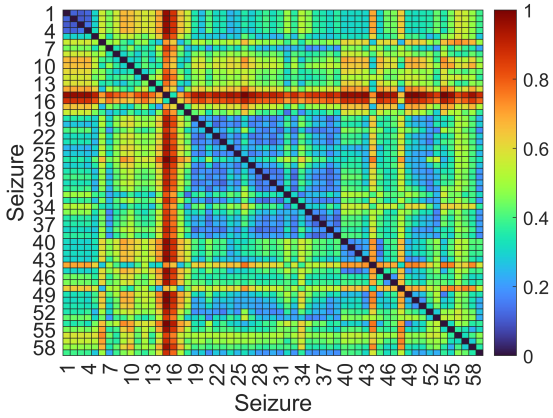
Demonstrated a clear clustering effect where seizures close in time were more similar, supporting our hypothesis (Pearson's $\rho = 0.10, p = 4.9 \cdot 10^{-9}$).



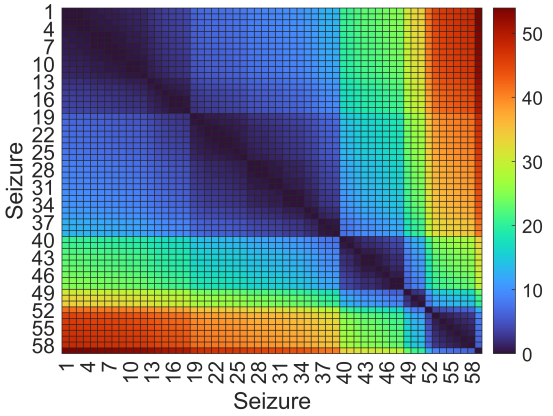
(a) The linear profile of subject's seizures.



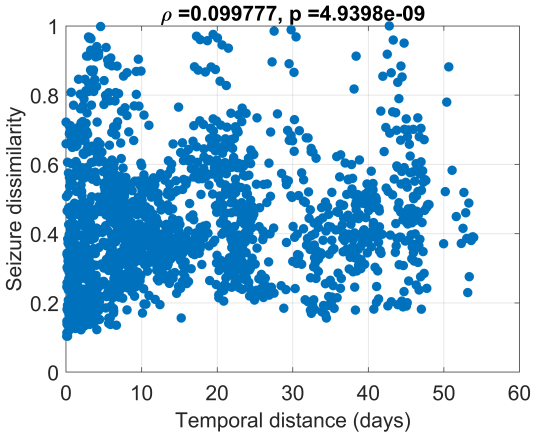
(b) Seizure pathways.



(c) Dissimilarity matrix.



(d) Temporal distance matrix.

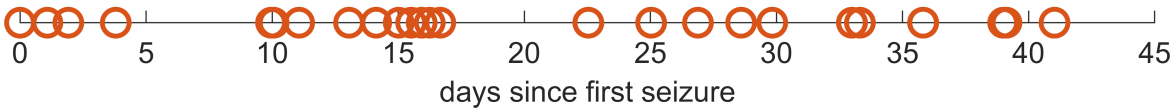


(e) Seizure dissimilarity vs. temporal distance.

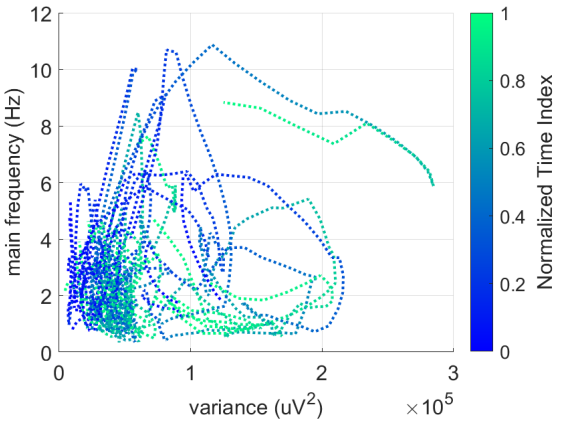
Figure 8: Analysis results for subject jc20190313_3.

3.2.9 Results for subject jc20190313_4

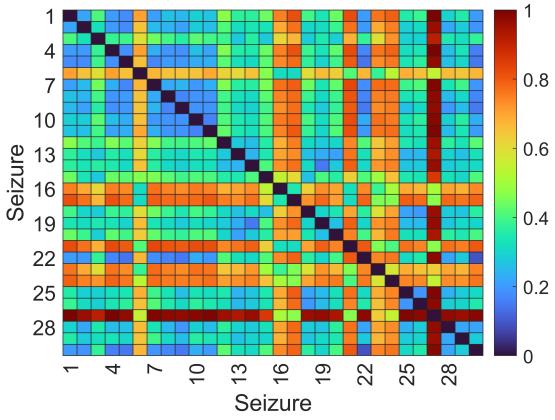
Many seizure clusters from the temporal distance matrix are visible also in the dissimilarity matrix. However, the Pearson's correlation is non-significant ($\rho = -0.008, p = 0.80$).



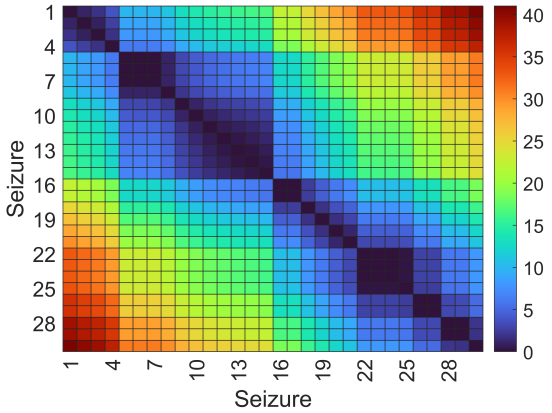
(a) The linear profile of subject's seizures.



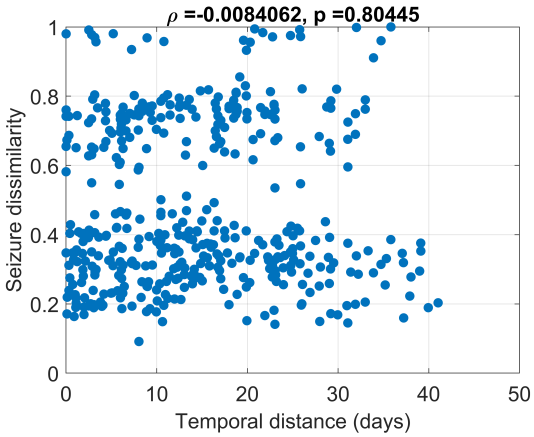
(b) Seizure pathways.



(c) Dissimilarity matrix.



(d) Temporal distance matrix.

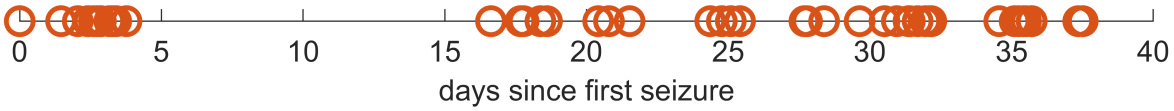


(e) Seizure dissimilarity vs. temporal distance.

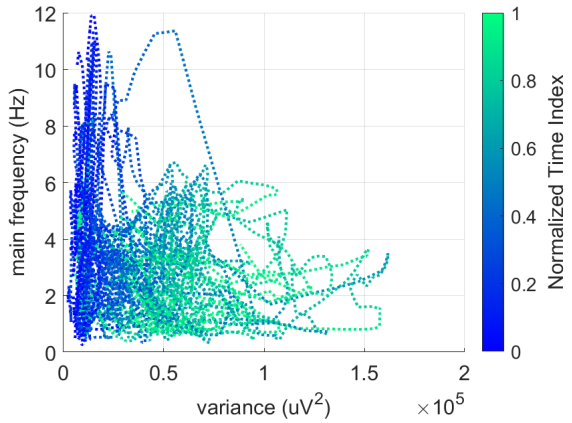
Figure 9: Analysis results for subject jc20190313_4.

3.2.10 Results for subject jc20190509_1

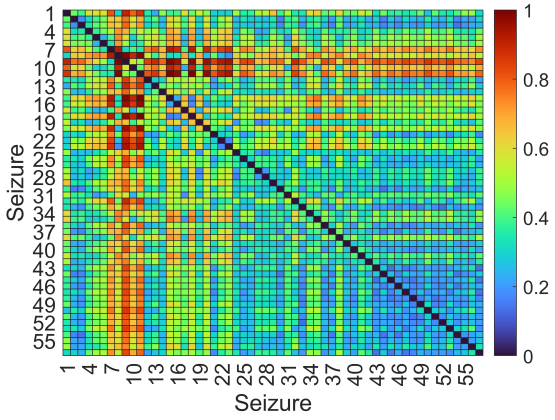
The analysis revealed a nuanced correlation pattern where temporal proximity and seizure similarity were more strongly correlated in later seizures, particularly evident in the lower right quadrant of the correlation analysis (Pearson's $\rho = 0.11, p = 1.9 \cdot 10^{-10}$). This suggests that as the study progressed, seizures that occurred closer together tended to be more similar, a pattern less pronounced in earlier seizures noted in the upper left quadrant.



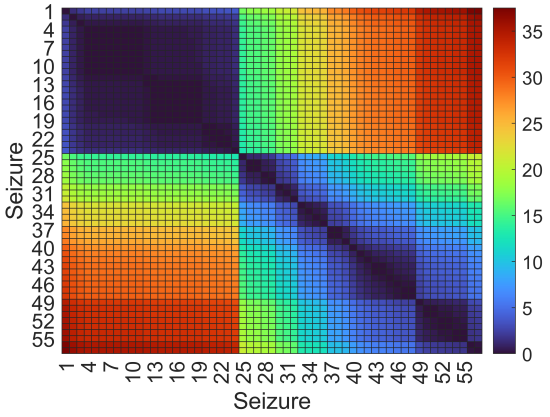
(a) The linear profile of subject's seizures.



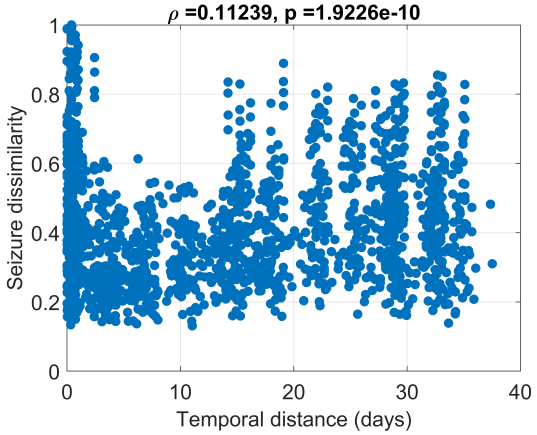
(b) Seizure pathways.



(c) Dissimilarity matrix.



(d) Temporal distance matrix.

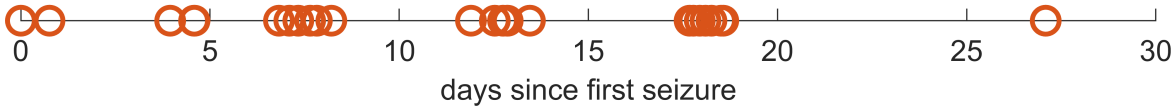


(e) Seizure dissimilarity vs. temporal distance.

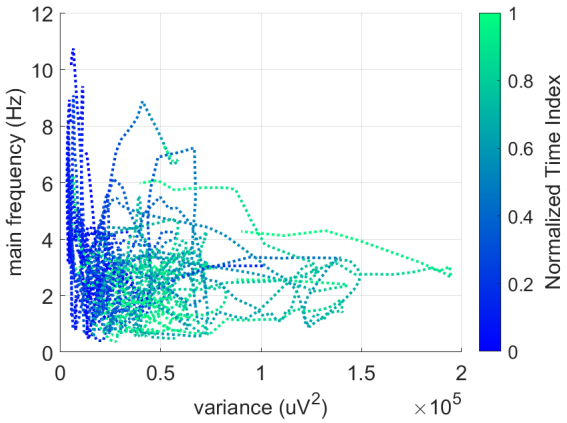
Figure 10: Analysis results for subject jc20190509_1.

3.2.11 Results for subject jc20190509_2

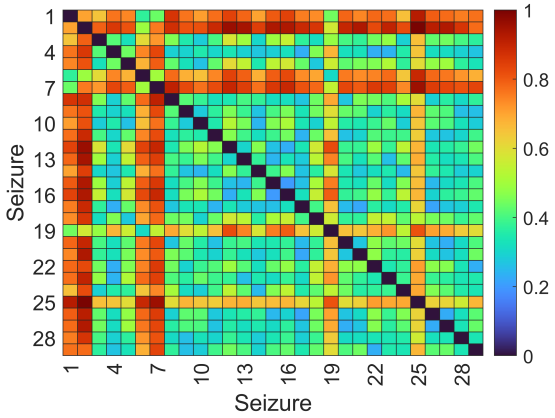
Demonstrated a clear clustering effect where seizures close in time were more similar, supporting our hypothesis (Pearson's $\rho = 0.20, p = 7.9 \cdot 10^{-9}$).



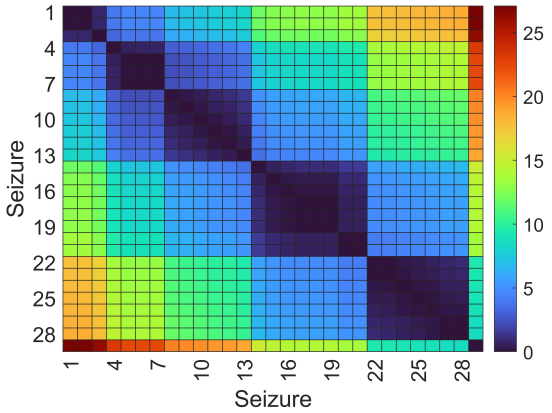
(a) The linear profile of subject's seizures.



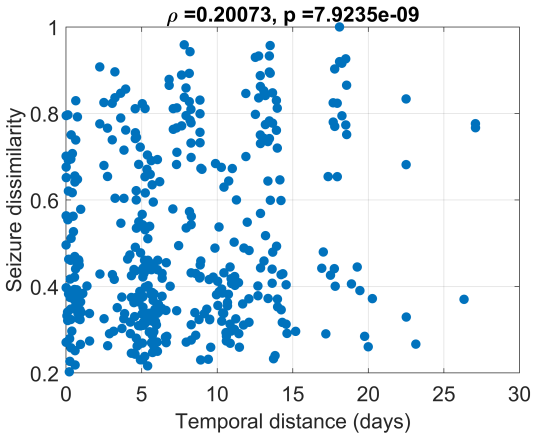
(b) Seizure pathways.



(c) Dissimilarity matrix.



(d) Temporal distance matrix.

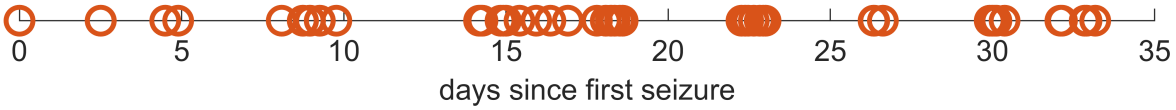


(e) Seizure dissimilarity vs. temporal distance.

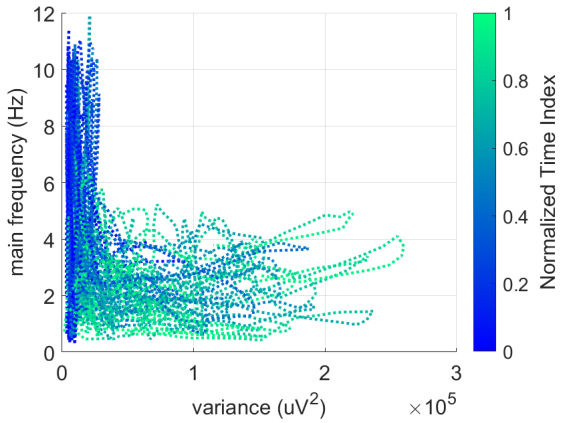
Figure 11: Analysis results for subject jc20190509_2.

3.2.12 Results for subject jc20190509_3

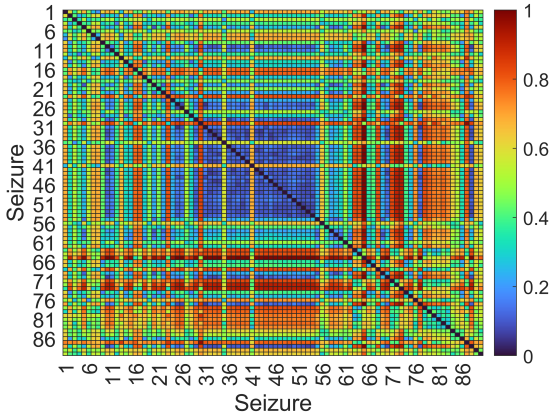
Exhibited a clear clustering effect and a strong correlation between the timing and characteristics of seizures, suggesting a stable seizure pattern (Pearson's $\rho = 0.23, p = 1.4 \cdot 10^{-96}$).



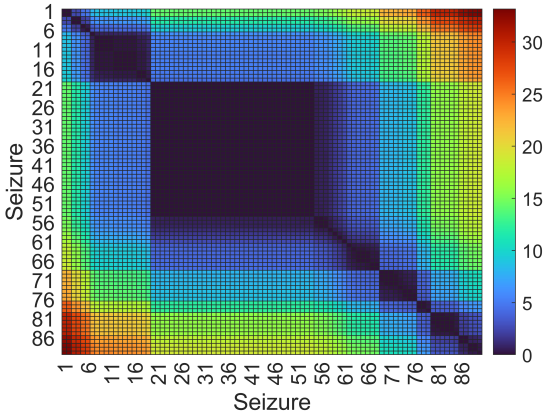
(a) The linear profile of subject's seizures.



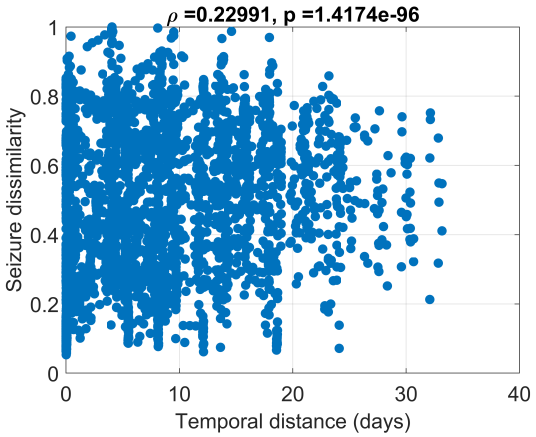
(b) Seizure pathways.



(c) Dissimilarity matrix.



(d) Temporal distance matrix.



(e) Seizure dissimilarity vs. temporal distance.

Figure 12: Analysis results for subject jc20190509_3.

Chapter 4
Discussion

The objective of this thesis was to test the hypothesis that seizures occurring closer in time exhibit more similar trajectories. This thesis utilizes a mouse model to explore the dynamic nature of seizure characteristics over time [8], using methods like DTW and dissimilarity matrix analysis. From the previous chapter we see, that the hypothesis was proved to be true in only 6 test subjects out of 11. Therefore, the result is inconclusive. Furthermore, there do not seem to be any discernible patterns in seizure characteristics that could explain the lack of a significant Pearson correlation between the timing and similarity of seizures.

However, by observing the dissimilarity matrices, I noticed oscillations of the values in time. That suggests that there could be another factor affecting seizure similarity than the temporal distance only. This variability in seizure pathways is consistent with Schroeder et al. [12], which illustrated that seizure pathways can vary in a cyclical manner based on circadian and slower timescales in individual patients with focal epilepsy. Furthermore, the high variability observed in seizure trajectories supports the hypothesis that epilepsy is highly individualistic, even in the highly controlled experimental conditions. This aligns with Schroeder et al.'s argument for personalized epilepsy management, reinforcing the need for customized treatment strategies that consider individual variability.

This research, while thorough, has its limitations. Firstly, the use of an animal model may not fully capture the human epileptic condition. The findings underscore the need for caution when extrapolating animal data to humans. Secondly, in contrast to Schroeder et al., I created seizure pathways from variance and the main frequency only. Expanding the seizure pathway analysis by more parameters and applying a multidimensional scaling could provide better and more precise results. And lastly, a different approach to obtaining the main frequency may prove useful. I opted for the calculation from the second highest peak of ACF due to the ACF's low susceptibility to noise. However, when working with complex waveforms, the estimation may be inaccurate. The first spectral moment may overcome this limitation in the complex waveforms such as epileptic EEG.

Future research should focus on identifying and quantifying the specific factors that influence the variability in seizure characteristics. This includes incorporating larger animal cohort, generating seizure pathways in an N-dimensional space of various characteristics, computing the first spectral moment instead of the main frequency, or conducting longitudinal studies that track changes in seizure dynamics in response to controlled environmental changes.

This study enhances our understanding of epilepsy's complexity and the variable nature of seizure manifestations. It supports the ongoing shift towards personalized medicine in epilepsy management, emphasizing the need to consider individual differences in seizure dynamics and response to treatment [12].

Chapter 5
Conclusion

This thesis aimed to explore the long-term evolution of seizure characteristics in a mouse model of epilepsy, employing advanced analytical techniques like dynamic time warping and a visualization of seizure pathways. The focus was on discerning patterns and variability in seizure dynamics to better understand the underlying mechanisms of epilepsy.

The study uncovered significant variability in seizure characteristics both within and across subjects, challenging the assumption that seizures in similar genetic backgrounds under controlled conditions would present homogeneously. Importantly, the findings suggested that temporal proximity does not always reliably predict seizure similarity, a revelation that may influence future approaches to seizure prediction and management

The insights gained from this research underscore the complexity of epilepsy and the need for personalized treatment strategies that account for the individual variability in seizure expressions. These findings pave the way for more sophisticated models that integrate diverse data types to predict and manage epilepsy more effectively.

In conclusion, this thesis has clinical relevance for epilepsy patients because what is true today may not be true tomorrow and therefore we need to know more about epilepsy, observe patients and apply the results to improve treatment. By embracing the variability and individuality of seizure dynamics, we can move closer to the ultimate goal of personalized medicine, offering tailored and effective interventions for those living with epilepsy.

References

[1] *Epilepsy*. World Health Organisation. 2023. URL: https://www.who.int/news-room/fact-sheets/detail/epilepsy (visited on 11/18/2023).

[2] Philip J. van der Eijk. "The 'theology' of the Hippocratic treatise On the Sacred Disease". In: *Medicine and Philosophy in Classical Antiquity*. Cambridge: Cambridge University Press, 2009, pp. 45–73. ISBN: 9780521818001. DOI: 10.1017/CBO9780511482670.004. (Visited on 11/18/2023).

[3] Robert S. Fisher et al. "ILAE Official Report: A practical clinical definition of epilepsy". In: *Epilepsia* 55 (4 2014), pp. 475–482. ISSN: 0013-9580. DOI: 10.1111/epi.12550. (Visited on 05/08/2024).

[4] Poonam Nina Banerjee, David Filippi, and W. Allen Hauser. "The descriptive epidemiology of epilepsy – A review," in: *Epilepsy Research* 85 (1 2009), pp. 31–45. ISSN: 0920-1211. DOI: 10.1016/j.eplepsyres.2009.03.003. (Visited on 11/19/2023).

[5] Roland D. Thijs et al. "Epilepsy in Adults". In: *The Lancet* 393 (10172 2019), pp. 689–701. ISSN: 0140-6736. DOI: 10.1016/s0140-6736(18)32596-0. (Visited on 11/19/2023).

[6] Shampa Ghosh et al. "Pharmacological and therapeutic approaches in the treatment of epilepsy". In: *Biomedicines* 9 (5 2021), p. 470. ISSN: 2227-9059. DOI: 10.3390/biomedicines9050470. (Visited on 04/27/2024).

[7] Dakota N. Crisp et al. "Quantifying epileptogenesis in rats with spontaneous and responsive brain state dynamics". In: *Brain Communications* 2 (1 2020). ISSN: 2632-1297. DOI: 10.1093/braincomms/fcaa048. (Visited on 11/20/2023).

[8] Jan Kudlacek et al. "Long-term seizure dynamics are determined by the nature of seizures and the mutual interactions between them". In: *Neurobiology of Disease* 154 (2021). ISSN: 0969-9961. DOI: 10.1016/j.nbd.2021.105347. (Visited on 11/20/2023).

[9] Philippa J. Karoly et al. "Cycles in epilepsy". In: *Nature Reviews Neurology* 17 (5 2021), pp. 267–284. ISSN: 1759-4766. DOI: 10.1038/s41582-021-00464-1. (Visited on 11/20/2023).

[10] Marc G. Leguia et al. "Seizure Cycles in Focal Epilepsy". In: *JAMA Neurology* 78 (4 2021), pp. 454–463. ISSN: 2168-6149. DOI: 10.1001/jamaneurol.2020.5370. (Visited on 11/20/2023).

[11] Alejo J. Nevado-Holgado et al. "Characterising the dynamics of EEG waveforms as the path through parameter space of a neural mass model: Application to epilepsy seizure evolution". In: *NeuroImage* 59 (3 2012), pp. 2374–2392. ISSN: 1053-8119. DOI: 10.1016/j.neuroimage.2011.08.111. (Visited on 11/22/2023).

[12] Gabrielle M. Schroeder et al. "Seizure pathways change on circadian and slower timescales in individual patients with focal epilepsy". In: *Proceedings of the National Academy of Sciences* 117 (20 2020), pp. 11048–11058. ISSN: 0027-8424. DOI: 10.1073/pnas.1922084117. (Visited on 11/20/2023).

Appendix A
Used software

- MATLAB [1] for code development.
- TexMaker [2] for writing this thesis.
- ChatGPT-4 [3] (OpenAI) for text style feedback and rephrasing suggestions in accordance with the *Methodological guideline No. 5/2023* [4].
- Open Signal Explorer and Labeller (OSEL) for visualization of EEG and its corresponding characteristics.

[1] https://www.mathworks.com/products/matlab.html
[2] https://www.xm1math.net/texmaker/
[3] https://chatgpt.com/
[4] https://www.cvut.cz/sites/default/files/content/d1dc93cd-5894-452-b799-c7e715d3c59e/en/20231003-methodological-guideline-no-52023.pdf