2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

# Phase-Amplitude Coupling Features Accurately Classify Multiple Sub-States Within a Seizure Episode

Vasily Grigorovsky, *Member, IEEE*

*Abstract*— **Epilepsy is frequently characterized by convulsive seizures, which are often followed by a postictal EEG suppression state (PGES). The ability to automatically detect and monitor seizure progression and postictal state can allow for early warning of seizure onset, timely intervention in seizures themselves, as well as identification of major complications in epilepsy such as status epilepticus and sudden unexpected death in epilepsy (SUDEP). To test whether it is possible to reliably differentiate these ictal and postictal states, we investigated 52 seizure records (both intracranial and scalp EEG) from 19 patients. Phase-amplitude cross-frequency coupling was calculated for each recording and used as an input to a convolutional neural network model, achieving the mean accuracy of 0.89±0.09 across all classes, with the worst class accuracy of 0.73 for one of the later ictal sub-states. When the trained model was applied to SUDEP patient data, it classified seizure recordings as primarily interictal and PGES-like state (70% and 26%, respectively), highlighting the fact that in SUDEP patients seizures primarily exist in postictal states and don't show the ictal sub-state evolution. These results suggest that using frequency coupling markers with a machine learning algorithm can reliably identify ictal and postictal sub-states, which can open up opportunities for novel monitoring and management approaches in epilepsy.**

## I. Introduction

Epilepsy is a disease characterized by synchronized neuronal activity, or seizures. While seizure etiologies and profiles might differ, convulsive seizures generally show a similar pattern of frequency evolution in time [1] and are followed by a state of reduced EEG activity – postictal EEG suppression (PGES) [2]. Research over the past decade has identified that the presence and duration of the PGES state is correlated with a risk of developing a fatal complication in epileptic patients – sudden unexpected death in epilepsy (SUDEP) [3].

The ability to accurately identify substates within a seizure episode is valuable for better epilepsy management. Being able to detect seizure early, either the immediate onset or an early stage of the seizure, provides an opportunity to alert the patient and increases the efficacy of anti-epileptic therapies [4]. Monitoring seizure progression can help predict the duration of the seizure early on and identify when seizure termination will occur. Since seizure duration is linked with the duration of the postictal state [5] – a state of cognitive and behaviour impairments [5], and exceedingly long seizures are classified as medical emergencies, early detection of a slow seizure evolution (i.e., a long-duration seizure) can provide better way to manage or prevent those complications. Finally, a recent study linked PGES duration with a seizure termination state [6], and so accurate classification of both seizure termination and the postictal state is important for assessing the risk of SUDEP in patients with epilepsy.

In an effort to analyze epileptic seizures, EEG signals are frequently decomposed into underlying frequency bands, or oscillations. These oscillations can be classified as low frequency oscillations (LFO's, <30 Hz) and high frequency oscillations (HFO's, >30 Hz). While these frequency bands are often looked at on their own, the coupling between LFO and HFO is an important part of both cognition [7], as well as a biomarker in epilepsy – phase-amplitude cross-frequency coupling (PAC) between low and high frequencies was successful in localizing epileptogenic zone [8], and preclinical seizure prediction [9]. Furthermore, the same coupling biomarkers were observed in computational model of neuroglial networks of epilepsy [10].

The objective of this study is to use phase-amplitude coupling features to reliably classify substates within a seizure episode, specifically during the seizure event as well as the postictal state. Furthermore, once a reliable algorithm is found, a secondary objective is to apply it to SUDEP patient data, in order to determine whether the frequency evolution of a seizure activity in SUDEP patients is similar to non-SUDEP ones, or the algorithm is able to differentiate two populations. We hypothesize that the algorithmic approach of using convolutional neural networks coupled with PAC's, will be able to reliably differentiate several substates within an ictal event and a separate postictal state.

## II. Methods

Data used in this study comes from several sources – the summary of the two main ones is shown in Table 1. EEG recordings – both scalp and intracranial – for the main portion of the study were obtained from a total of 19 patients. One cohort of eight patients came from the University of Penn and Mayo Clinic dataset (UPMC) which was part of a Kaggle competition, and it had a total of 26 intracranial seizure recordings with durations varying between 10 and 120 seconds, as well as substantial interictal and unlabeled data [4]. The second cohort came from a combination of iEEG and scalp EEG recordings from Toronto Western Hospital (TWH, Toronto, Canada) and Phramongkutklao Hospital (PH, Bangkok, Thailand) of 11 patients with 26 seizures [1]. Notably, this cohort had longer seizures and a

*Research was generously supported by Canadian Institutes of Health Research (CIHR), Ontario Brain Institute (OBI), and National Sciences and Engineering Research Council (NSERC)

V. Grigorovsky was with the Institute of Biomedical Engineering, University of Toronto, ON M5S3G9 Canada (e-mail: vasily.grigorovsky@utoronto.ca).

*Table 1: Patient data summary*

| Data Source | Number of Patients | Total Ictal Seconds | Number of Seizures | Seizure Duration Range | Total Interictal Seconds | Total Unlabelled Seconds | PGES Duration Range | Original Sampling Frequency | Notes |
|---|---|---|---|---|---|---|---|---|---|
| UPMC [4] | 8 | 1390 | 26 | 10 – 120 sec | 14329 | 19274 | N/A | 500 – 5000 Hz | |
| TWH/PH [1] | 11 | 1716 | 26* | 21.5 – 99 sec | 2239 | N/A | 4.2 – 39 sec | 200 – 2000 Hz | * Including scalp EEG |

larger overall duration of ictal activity compared to cohort 1; as well as it specifically included postictal EEG suppression (PGES) state after each seizure.

Following the protocol in Grigorovsky et al. [1], the data was filtered with a 0.1 Hz high pass filter during the acquisition, and power line interference was removed using FIR notch filter (focusing on 50 Hz or 60 Hz and the associated harmonics depending on where the data came from). The data was then downsampled with anti-aliasing to 200 Hz for consistency.

After pre-processing, the data was used to find phase-amplitude cross-frequency coupling (PAC) following the protocol in Grigorovsky et al. [1]. Briefly, using complex Morlet wavelet (center frequency 0.8125 Hz; 5Hz bandwidth) wavelet coefficients were extracted from the demeaned EEG data. Wavelet coefficients were then split into two groups – a high frequency group ($f_H$, 30-100 Hz in 1 Hz increments) and a low frequency group ($f_L$, 1-15 Hz in 0.5 Hz increments). These frequencies were chosen as they are commonly used in epilepsy phase-amplitude coupling research [8, 9]. Two separate time series were then recreated from these groups – the amplitude envelope signal $A(\hat{t}, f_H)$, and the phase signal $\varphi(\hat{t}, f_L)$. The phase signal was then binned into 18 bins of 20° each, and amplitude envelope signal was averaged over each bin. This averaged amplitude was normalized across all bins, and the degree of deviation of this distribution of normalized average amplitudes from a uniform distribution was the PAC.

This PAC computation was done on one-second windows. During sensitivity testing, one cycle of the lowest frequency (1 Hz) was found to be enough to capture the PAC features. Reducing the window of analysis was important to better detect specific times within the seizure evolution. For each such PAC window, a latency parameter was assigned, marking the progression of the seizure (from an electrographic onset determined by a neurologist), starting with 1 second. As a matter of convention, the latency was set to 0 for an interictal recording, and to -1 for a postictal suppression state. To increase the available data, PAC for each channel was treated as a separate data point; however, to reduce the effects of potential artifacts, a global PAC across all channels was added as a second input.

In this study, PAC's were used together with a convolutional neural network (CNN) which comprised of three feature-extracting convolutional layers (each with batch normalization and rectified linear unit (ReLU) a non-linear activation function) and two fully connected multi-layer perceptron layers (MLP, see Figure 1). Batch normalization is a regularization technique that normalizes values of each of the layer, reducing the dependence of the layer on the mean and variance of other layers in the network [11]. The two MLP layers had a dropout factor of 0.5, in an effort to reduce overfitting.

Using 5-fold cross-validation, the model was trained on the available ictal and interictal data from the UPMC dataset. As the initial dataset is unbalanced, rebalancing measures were used, such as oversampling of ictal data and undersampling of interictal data. In order to take advantage of extra unlabelled data, for which the latency class was not known, we applied a pseudo-labelling technique – a semi-supervised learning approach where unlabelled PAC's get assigned latency classes generated by previously trained model.

Together with ictal and interictal data, these pseudo-labelled PAC's were combined with the data from TWH and PH, and the model was re-trained again using 5-fold cross-

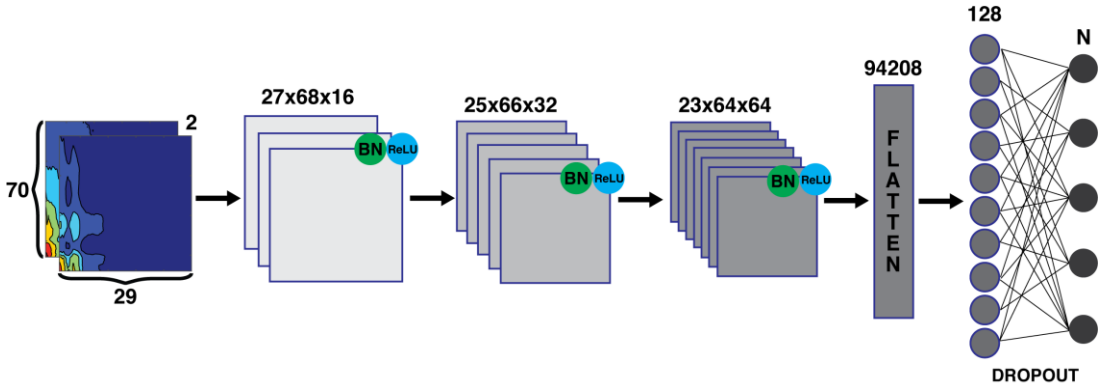


*Figure 1: Graphical representation of the convolutional neural network used in the study. The network consists of three convolutional layers followed by two layers of feedforward artificial neural networks. Batch normalization (BN) is applied at all of the convolutional layers. Dropout is used to reduce model overfitting before the final output layer. The output layer has N units, as the number of classes was varied during the study. All layers other than the output layer use ReLU activation function.*

validation – resulting in the total of 52 seizures from 19 patients, with 15 scalp EEG recordings and 42 intracranial EEG recordings. Furthermore, 26 seizures had the postictal EEG suppression (PGES) state. Altogether, this amounted to 39494 1-second phase-amplitude coupling comodulograms.

*Table 2: SUDEP patient data*

| Patient | Recording length | Type | Sampling Frequency |
|---|---|---|---|
| **P1** | 820 sec | iEEG | 1000 Hz |
| **P1** | 820 sec | scalp | 1000 Hz |
| **P2** | 1000 sec | iEEG | 512 Hz |
| **P2** | 1800 sec | scalp | 256 Hz |
| **P3** | 140 sec | scalp | 256 Hz |

In order to test the model's performance on SUDEP patients, PAC's were extracted from five EEG recordings, each one containing at least one seizure as identified by clinicians (SUDEP data summary listed in Table 2). For all of the training, a stochastic gradient descent was used, with batch size of 32. Keras machine learning library was used for this analysis. As this was a multi-class classification task, a confusion matrix was used which highlighted the classes that were well-predicted and which labels were difficult for the model to accurately classify. An overall accuracy measure was defined as the average fraction of correct predictions extracted from the confusion matrix. All of the data processing, analysis, and modelling was done in Python.

## III. Results

While the trained CNN model was briefly investigated for individual latency classification (results not shown), due to widely varied seizure durations the study focused on binning latencies and classifying the bins instead. When ictal data from both sources – UPMC, as well as TWH+PH – was binned into ten 1-second intervals, the mean accuracy of classification was 0.78±0.19, with the lowest accuracy of 0.30, and highest accuracy of 1.0 (see Figure 2). Since maximum seizure duration is 120 seconds, there are 12 classes, in addition to class 0 (interictal data). The results showed that interictal data was easily classifiable, while longer-duration seizure terminations were more difficult to classify accurately – likely due to smaller number of long (100+ second) seizures.

Another approach was to subdivide ictal PAC's into groups that are relative to the overall seizure duration, as opposed to an absolute latency binning. Following the substate separation suggested by the seizure detection competition for which UPMC data was collected, the seizure state was subdivided into early ictal (first 20% of latencies) and ictal (the rest of ictal PAC's) substates. When combined with interictal and postictal states, for all of the data the model showed mean accuracy of 0.83±0.34; with the lowest substate classification accuracy of 0.31, and the highest of 1.0 (see Figure 3A).

When instead the ictal state is subdivided into quartiles (e.g. first 25% of seizure latencies), across all of the patients' data the mean accuracy increases to 0.89±0.09, and the minimal substate classification accuracy increases to 0.73; with the highest remaining at 1.0 (Figure 3B).

Once trained, the model was applied to SUDEP patient data. Since one of the hypotheses of this study is that SUDEP patients' recordings do not display the same frequency variation as non-SUDEP ones, SUDEP data analysis was performed slightly different – instead of finding the accuracy of model's class predictions, the most likely state was identified for each PAC. As the example classification in Figure 3C shows, the model identifies primarily interictal (class 0) and PGES (class 5) states throughout the event recording. Overall, across all five recordings, the model classified 70% of PAC's as interictal, and 26% of PAC's as PGES-like state, which is consistent with case-study findings using hidden Markov model [1].

## IV. Discussion

Our results show that when using phase-amplitude coupling as features for a convolutional neural network, the model is able to reliably identify seizure onset and differentiate a variable number of sub-states within a seizure. Furthermore, with this EEG sub-state classification, the model highlighted the differences between SUDEP and non-SUDEP patients, suggesting a potential for early warning and intervention for at-risk patients.

Out of the setups tried in this study, subdividing the ictal latencies into four different quartiles (resulting in a 6-state model) showed the best overall accuracy with lowest variability across classes. This is likely because the 4-state model had trouble differentiating the early ictal from the later ictal sub-states (note that the threshold of what constitutes an early seizure varied somewhat from the original competition); while the 13-state model with ictal latency binning had low accuracy for seizure timings of 100-120 seconds, since there were not a lot of long-duration seizures. Importantly, both

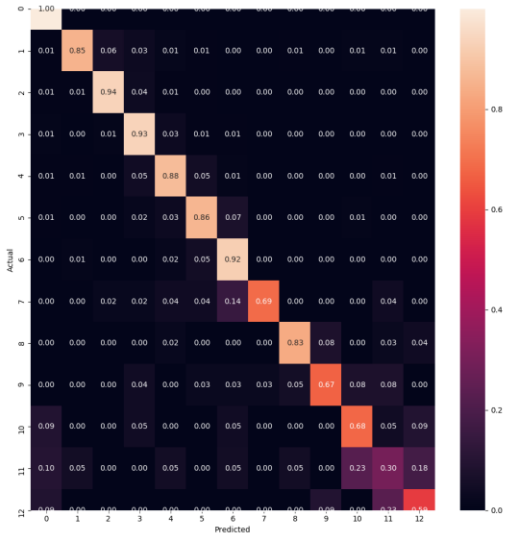


*Figure 2: Results of a CNN model classification of all ictal and interictal PAC's. PAC's were classified into interictal (class 0), or each of the 10 1-second bins (e.g. 1-10 seconds, 11-20 seconds, etc.) of the ictal event. Due to lower number of long-duration seizures, the model showed worse performance in the higher end of ictal latencies. Overall accuracy was 0.79±0.19.*

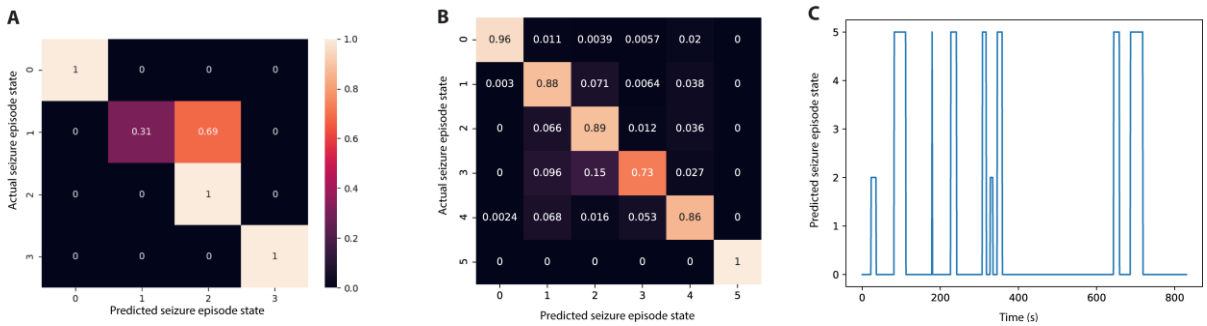


*Figure 3: Results of CNN classification, and SUDEP analysis. A) Confusion matrix of a four state (interictal, early ictal, late ictal, and postictal state) classification – mean accuracy of 0.83±0.34. The trained algorithm had no problem classifying interictal, ictal, and postictal states, however the model has trouble separating the early ictal state from the rest of ictal data. B) Confusion matrix for a six-state classification (interictal, first, second, third, and fourth quartiles of a seizure, as well as postictal state) – mean accuracy of 0.89±0.09. Overall, there is much less confusion of the model, with only slight confusion between the middle two quartiles of the ictal state. C) Classification of an example iEEG SUDEP trace (shown in [1]) using the six-class CNN model. The model identifies primarily interictal and PGES-like states, capturing the predominance of postictal states in SUDEP patients.*

models in Figure 3 classified PGES states without error, differentiating them from both ictal and interictal states – a finding that is important for SUDEP risk monitoring.

This preliminary model can be improved in several ways. EEG is at its core a time-series signal, which suggests that incorporating a machine learning algorithm optimized for sequence data, such as long short-term memory (LSTM), could improve classification accuracy – an LSTM-based model has been successfully used in seizure prediction tasks [12]. Another avenue for improvement is incorporating both very high frequency oscillations (500+ Hz) and very low frequencies (0.1 – 1 Hz) in the PAC calculation, as both have been found to have a potential to act as a biomarker in pathological brain conditions [13]. While utilizing very low frequencies increases the minimum time window used, for longer-duration seizures the benefits of such analysis will likely outweigh the loss of granularity. Yet another approach is to include additional inputs into model, such as EKG and EMG, since both have been used for seizure detection previously [14, 15].

Being able to quickly and reliably classify sub-states of a seizure opens up opportunities to modulate these seizures better, for example using neuromodulation to prevent the ictal event from spreading. Better ictal substate classification, especially with clear and understandable features used as inputs, can also help shed light on some of the underlying mechanisms and phenomena of seizure propagation and termination.

Since exceedingly long seizures such as status epilepticus constitute a medical emergency, the ability for an early detection of irregular ictal sub-state transition (such as continuing first ictal quartile, or regression from later quartiles to earlier ones) can allow patients and medical professionals to seek treatment ahead of said emergency. While different in etiology, this lack of expected ictal state evolution is also observed in SUDEP patients, a fact that, together with recent findings linking it with refractory status epilepticus (RSE), and New-Onset RSE (NORSE) [16], highlights the importance of investigating PAC-based techniques for monitoring complications in epilepsy and potentially identifying targets for novel therapeutic approaches.

## REFERENCES


[1] V. Grigorovsky, et al., "Delta-gamma phase-amplitude coupling as a biomarker of postictal generalized EEG suppression", *Brain Comm*, vol. 2(2), pp. 1-16, 2020.

[2] R. Surges, et al., "Postictal generalized electroencephalographic suppression is associated with generalized seizures," *Epilepsy Behav*, vol. 21, pp. 271–274, 2011

[3] S. D. Lhatoo, et al., "An electroclinical case-control study of sudden unexpected death in epilepsy," *Ann. Neurol.*, vol. 68, no. 6, pp. 787–796, 2010.

[4] S. N. Baldassano, et al., "Crowdsourcing seizure detection: algorithm development and validation on human implanted device recordings", *Brain*, vol. 140, pp. 1680-1691, 2017.

[5] J. Ohira, et al., "Factors associated with the duration of the postictal state after a generalized convulsion", *Seizure*, vol. 65, pp. 101-105, 2019.

[6] P. R. Bauer, et al., "Dynamics of convulsive seizure termination and postictal generalized EEG suppression", *Brain*, vol. 140, pp. 655-668, 2017.

[7] J.E. Lisman, O. Jensen, "The Theta-Gamma Neural Code," *Neuron*, vol. 77, no. 6, pp. 1002-1016, 2014.

[8] M. Guirgis, et al, "Defining regions of interest using cross-frequency coupling in extratemporal lobe epilepsy patients," *J. Neural Eng.*, vol. 12, no. 2, p. 26011, 2015.

[9] D. Jacobs, et al., "Classification of Pre-Clinical Seizure States using Scalp EEG Cross-Frequency Coupling Features", *IEEE Trans Biomed Eng*, vol. 65, no. 11, pp. 2440-2449, 2018.

[10] V. Grigorovsky, et al., "Glial Modulation of Electrical Rhythms in a Neuroglial Network Model of Epilepsy," *IEEE Trans Biomed Eng*, vol. NA, no. NA, pp. 1-12, 2020.

[11] S. Ioffe, C. Szegedy, "Batch Normalization: Accelerating Deep Network Training by Reducing Internal Covariate Shift". In: *arXiv:1502.03167 [cs]* (Mar. 2015). arXiv: 1502.03167.

[12] K. M. Tsiouris, et al., "A Long Short-Term Memory deep learning network for the prediction of epileptic seizures using EEG signals", *Comput Biol Med.,* vol. 99, pp. 24-37, 2018.

[13] V. Grigorovsky, et al., "Machine Intelligence-Based Epileptic Seizure Forecasting," in *Neural Engineering*, Cham: Springer International Publishing, 2020, pp. 535–565.

[14] Ivan Osorio, "Automated seizure detection using EKG", *Int. J Neur Sys,* vol. 24, no. 2, pp. 1450001, 2014.

[15] S. Beniczky, et al., "Automated real-time detection of tonic-clonic seizures using a wearable EMG device," *Neurology*, vol. 90, pp. 428-434, 2018.

[16] L. J. Hirsch et al. "Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions," *Epilepsia*, vol. 59, no. 4, pp. 739-744, 2018