

1 Phase-amplitude coupling for detection and prediction
2 of epileptic seizures in long-term intracranial
3 electroencephalogram data

4 Yusuke Watanabe^a, Takufumi Yanagisawa^{b,c}, David B. Grayden^{a,*}

5 ^a*NeuroEngineering Research Laboratory, Department of Biomedical Engineering, The*
6 *University of Melbourne, Parkville VIC 3010, Australia*

7 ^b*Institute for Advanced Cocreation studies, Osaka University, 2-2 Yamadaoka, Suita,*
8 *565-0871, Osaka, Japan*

9 ^c*Department of Neurosurgery, Osaka University Graduate School of Medicine, 2-2*
10 *Yamadaoka, Osaka, 565-0871, Japan*

11 **Abstract**

12
13 Neural oscillations exhibit complex cross-frequency interactions that are
14 fundamental to brain function and disrupted in neurological disorders. Phase-
15 amplitude coupling (PAC), where the phase of low-frequency oscillations
16 modulates the amplitude of high-frequency activity, serves as a biomarker
17 for various brain states including epileptic seizures. Previous studies have
18 demonstrated PAC changes around seizure events, but comprehensive char-
19 acterization across extended timescales remains limited due to the scarcity
20 of long-term recording data and computational constraints. The challenge
21 of processing continuous, long-term neural recordings has hindered the de-
22 velopment of reliable seizure prediction systems. Here we show that GPU-
23 accelerated PAC computation enables comprehensive analysis of 4.1 TB of
24 continuous intracranial electroencephalogram data from 15 patients with fo-
25 cal epilepsy (NeuroVista dataset), encompassing 1,539 seizures over monitor-
26 ing periods ranging from 6 months to 2 years. We found distinct PAC signatures between theta-to-
27 achieving balanced accuracy of 0.55 ± 0.04 and ROC-AUC of 0.58 ± 0.02 for
28 discriminating pre-ictal from interictal states. Our GPU-accelerated imple-
29 mentation achieved 100-fold speed improvements compared to conventional

CPU-based methods, reducing computation time from years to months and potentially enabling real-time PAC monitoring with less than 2-minute processing latency. These findings reveal that continuous PAC monitoring captures seizure-related neural dynamics with sufficient lead time for clinical intervention, although moderate classification performance indicates the need for multimodal biomarkers. The computational framework and temporal PAC patterns identified here provide a foundation for next-generation implantable seizure advisory systems, potentially improving quality of life for millions with drug-resistant epilepsy through reliable seizure warnings integrated with patient-specific therapeutic interventions.

Keywords: epilepsy, seizure detection, seizure prediction, NeuroVista dataset, phase-amplitude coupling

~ 1 figures, 0 tables, 271 words for abstract, and 3600 words for main text

1. Introduction

Epilepsy affects approximately 70 million people worldwide, representing one of the most prevalent neurological disorders characterized by recurrent, unpredictable seizures that fundamentally disrupt daily life and impose substantial societal burden **??**. Drug-resistant focal epilepsy, occurring in approximately 30-40% of epilepsy patients, remains particularly challenging as conventional antiepileptic medications fail to provide adequate seizure control despite optimal medical management **??**. The development of reliable seizure prediction systems represents a critical frontier in epilepsy care, offering the potential to transform patient management from reactive treatment to proactive intervention, thereby reducing seizure-related injuries, psychological burden, and improving quality of life for millions of individuals with drug-resistant epilepsy **??**.

Decades of research have established that neural oscillations exhibit complex cross-frequency interactions fundamental to brain function, with phase-

59 amplitude coupling (PAC) emerging as a robust biomarker for various brain
60 states including pathological conditions **??**. PAC quantifies the phenomenon
61 whereby the phase of low-frequency oscillations modulates the amplitude of
62 high-frequency activity, reflecting coordinated neural communication across
63 different temporal scales essential for cognitive processes and sensorimotor
64 integration **??**. Previous electrophysiological studies have demonstrated
65 measurable PAC alterations in the peri-ictal period, with changes in theta-
66 gamma coupling patterns observed minutes to hours before seizure onset
67 in both animal models and human patients **??**. However, comprehensive
68 characterization of PAC dynamics across extended timescales has remained
69 limited due to the computational demands of processing continuous, long-
70 term neural recordings and the relative scarcity of datasets spanning months
71 to years of continuous monitoring **??**.

72 Existing seizure prediction approaches, including both traditional PAC-
73 based methods and contemporary machine learning techniques, face several
74 critical limitations that have hindered clinical translation. While current
75 trends favor deep learning and complex feature extraction algorithms, these
76 approaches often suffer from poor interpretability, extensive hyperparamete-
77 ter optimization requirements, and limited generalizability across patients
78 and recording conditions **??**. Traditional PAC-based seizure prediction
79 approaches specifically face computational constraints that have restricted
80 most studies to short recording segments or sparse temporal sampling, pre-
81 venting comprehensive analysis of PAC evolution across full seizure cycles
82 and missing potentially crucial long-term patterns **??**. Methodological in-
83 consistencies in PAC quantification, including variations in frequency band
84 definitions, modulation index calculations, and statistical normalization ap-
85 proaches, have produced conflicting results across studies and limited repro-
86 ducibility **??**. Additionally, the majority of previous investigations have
87 relied on relatively small datasets with limited seizure counts per patient,
88 reducing statistical power and generalizability of findings to diverse epilepsy
89 phenotypes **??**. Finally, conventional CPU-based implementations of PAC

algorithms exhibit prohibitive computational complexity for real-time applications, with processing times often exceeding recording duration by orders of magnitude, making continuous monitoring clinically impractical ??.

These limitations underscore the critical need for a computationally efficient, comprehensive approach to PAC-based seizure prediction that can leverage large-scale, long-term electrophysiological datasets to identify robust, generalizable biomarkers of seizure susceptibility with sufficient temporal resolution for clinical intervention.

To address these challenges, we developed a GPU-accelerated PAC computation framework optimized for massive-scale electrophysiological data analysis, enabling comprehensive characterization of phase-amplitude coupling dynamics across 4.1 terabytes of continuous intracranial electroencephalogram (iEEG) recordings from the NeuroVista dataset. Our approach leverages the Spartan HPC system’s distributed GPU architecture with custom PyTorch implementations achieving approximately 100-fold acceleration compared to conventional CPU methods. PAC offers distinct advantages over conventional machine learning biomarkers as it reflects fundamental neural communication mechanisms without requiring hyperparameter optimization, providing inherently interpretable measures of cross-frequency interactions essential for brain functioning ?. We applied this framework to analyze 1,539 Type 1 seizures across 15 patients with drug-resistant focal epilepsy, examining PAC evolution from 24 hours before to 10 minutes after seizure onset using adaptive temporal sampling with 1-minute resolution windows. Statistical robustness was ensured through surrogate-based normalization using 200 circular phase shuffles, generating stable z-scored PAC features within each temporal window that maintain statistical validity across extended monitoring periods.

Our analysis revealed systematic modulation of theta-to-beta phase (2-30 Hz) and gamma amplitude (60-180 Hz) coupling patterns occurring 5-60 minutes before seizure onset, achieving balanced accuracy of 0.55 ± 0.04 and area under the receiver operating characteristic curve of 0.58 ± 0.02 for discrimi-

121 nating pre-ictal from interictal states. The GPU-accelerated implementation
122 reduced computation time from years to months while maintaining statis-
123 tical rigor through surrogate-based significance testing, demonstrating the
124 feasibility of near real-time PAC monitoring with processing latencies under
125 2 minutes.

126 These findings establish PAC as a computationally tractable biomarker
127 for seizure prediction in large-scale clinical datasets, providing a founda-
128 tion for next-generation implantable advisory systems that could transform
129 epilepsy management from reactive to predictive care. The moderate classi-
130 fication performance observed highlights the need for multimodal biomarker
131 integration while demonstrating sufficient predictive capacity to warrant clin-
132 ical investigation of PAC-based seizure warning systems.

133 2. Methods

134 2.1. Dataset and Study Design

135 Data were obtained from the NeuroVista clinical trial ?? through the
136 International Epilepsy Electrophysiology Portal (ieeg.org). The dataset com-
137 prised continuous intracranial electroencephalogram (iEEG) recordings from
138 15 human subjects with drug-resistant focal epilepsy, collected under ethical
139 approval from the original clinical trial ?. Each subject was implanted
140 with 16-channel platinum-iridium electrode arrays positioned around the
141 clinically-identified seizure onset zone, with signals sampled at 400 Hz and
142 wirelessly transmitted to an external personal advisory device. The total
143 dataset encompassed 4.1 TB of continuous recordings, with individual mon-
144 itoring periods ranging from 6 months to over 2 years. From the complete
145 dataset containing multiple seizure types, this study specifically analyzed
146 1,539 Type 1 (clinical) seizures with verified clinical manifestations across
147 the 15 patients to ensure clinical relevance and interpretability of prediction
148 algorithms.

149 Seizures were classified following the original trial protocol into clinical
150 (Type 1), clinically-equivalent (Type 2), and subclinical (Type 3) events.

151 For this study, we focused exclusively on Type 1 seizures, which presented
 152 with observable clinical symptoms and clear electrographic patterns. Type 2
 153 events (seizure-like events without clinical manifestations) and Type 3 events
 154 (subclinical seizures with distinct electrographic signatures) were excluded
 155 from analysis to maintain clinical relevance and ensure clear interpretation of
 156 prediction performance. Interictal control periods were selected from seizure-
 157 free intervals exceeding 4 hours from any Type 1 seizure event, matched for
 158 time of day to control for circadian influences on neural oscillations.

159 *2.2. Data Preprocessing and Quality Control*

160 The entire dataset was split into training, validation, and test sets fol-
 161 lowing temporal progression to ensure pseudo-prospective evaluation. This
 162 temporal separation between training and testing phases prevents data leak-
 163 age and provides realistic assessment of prediction performance. Training
 164 data comprised the earliest recordings, followed by validation data for hyper-
 165 parameter tuning, with the most recent recordings reserved as held-out test
 166 data.

167 Data integrity was maintained through cryptographic hashing (SHA-256)
 168 of all iEEG segments and seizure identifiers, enabling complete traceability
 169 and reproducibility of analyses. Each processed segment was stored with
 170 metadata including patient identifier, seizure type, exact timing, channel
 171 configuration, and processing parameters.

172 *2.3. Phase-Amplitude Coupling Analysis*

173 *2.3.1. GPU-Accelerated Implementation*

174 PAC strength was quantified using the modulation index (MI) [?] follow-
 175 ing the Shannon entropy-based formulation: $MI = 1 + (p \times \log(p))/\log(N)$,
 176 where p represents the normalized amplitude distribution across N phase bins
 177 and $N = 18$ bins (20° per bin). Computation was performed using a custom,
 178 standalone GPU-accelerated package (<https://github.com/ywatanabe1989/gPAC>)
 179 built on PyTorch with full vectorization across all frequency combinations.
 180 The implementation achieved approximately 100-fold speed improvement

181 compared to conventional CPU-based methods through: (1) massive tensor
 182 operations eliminating nested loops, (2) optimized memory allocation utiliz-
 183 ing up to 320GB total VRAM across multiple GPU nodes, and (3) batch
 184 processing with fp16 precision where appropriate. Processing leveraged the
 185 Spartan HPC system’s distributed GPU architecture ?? with automatic
 186 multi-GPU parallelization. Statistical significance was established using 200
 187 surrogate datasets generated through circular phase shuffling, with PAC val-
 188 ues z-score normalized relative to the surrogate distribution to eliminate spu-
 189 rious coupling.

190 For each 1-minute non-overlapping time window, PAC was computed be-
 191 tween 25 phase frequency bands (2.0-30.0 Hz) and 25 amplitude frequency
 192 bands (60.0-180.0 Hz), resulting in a 625-element PAC matrix per channel
 193 per time point. Frequency bands were generated using field-standard adap-
 194 tive bandwidths: phase bands employed bandwidth = $f/2$ (e.g., 10 Hz center
 195 frequency spans 7.5-12.5 Hz), while amplitude bands used bandwidth = $f/4$
 196 (e.g., 100 Hz center frequency spans 87.5-112.5 Hz). This approach yielded
 197 phase bands with bandwidths ranging from 0.5 Hz to 11.9 Hz and ampli-
 198 tude bands with bandwidths from 7.5 Hz to 40.0 Hz. Phase and amplitude
 199 information were extracted through bandpass filtering followed by Hilbert
 200 transformation to obtain instantaneous phase and amplitude envelopes. MI
 201 quantified coupling strength using the Shannon entropy-based formulation
 202 across 18 phase bins (20° each):

$$MI = 1 + \frac{\sum_{j=1}^N p_j \log(p_j)}{\log(N)} \quad (1)$$

203 where p_j represents the normalized amplitude probability in phase bin j ,
 204 and $N = 18$ indicates the number of phase bins. Values range from 0 (uniform
 205 amplitude distribution) to 1 (maximum concentration in single phase bin).
 206 PAC values were z-score normalized using 200 surrogate datasets generated
 207 through circular phase shifts to control for spurious coupling effects.

208 Missing values (NaN) in PAC computations arose from NaN values in
 209 recorded ECoG signals due to limited data type (int16), edge effects in fil-

tering, or numerical instabilities in specific frequency combinations. NaN values found in ECoG signals were replaced with 0 while NaN values in PAC data were handled as is. Features derived from PAC matrices used nanmean, nanstd, and other NaN-aware statistical functions from NumPy to ensure robust computation despite missing values.

2.3.2. Temporal Windows and Event Definition

PAC dynamics were analyzed across multiple temporal scales relative to seizure onset. For each seizure event, computations spanned from -1440 minutes (24 hours) to +10 minutes post-onset, with adaptive temporal resolution optimized for seizure prediction. Timestamps relative to seizure onset ($t = 0$) were generated using conditional sampling:

$$t_i = \begin{cases} -\text{round}(10^{(\log_{10}(60) + i \cdot \frac{\log_{10}(1440) - \log_{10}(60)}{N_{log} - 1})}) & \text{for } i = 0, 1, \dots, N_{log} - 1 \text{ (logarithmic)} \\ -60 + j & \text{for } j = 0, 1, \dots, 70 \text{ (linear)} \end{cases} \quad (2)$$

where logarithmic sampling from -1440 to -60 minutes provides denser resolution approaching seizure onset, and minute-by-minute linear sampling from -60 to +10 minutes captures critical peri-ictal to early ictal dynamics. The pre-ictal period was operationally defined as -60 to -5 minutes before seizure onset, based on previous seizure prediction studies [??](#) and clinical requirements for actionable warning times.

For each Type 1 seizure, an equal number of interictal control segments were randomly sampled from the available seizure-free periods (>4 hours from any Type 1 seizure), ensuring balanced representation in subsequent classification analyses. Control segments were matched for time of day to account for circadian variations [\[? \]](#) in PAC patterns. All random sampling employed fixed seeds (SHA-256 hash-based) for complete reproducibility across analyses.

234 2.4. Database Architecture and Storage

235 Processed PAC data were organized in patient-specific SQLite3 databases
236 with hierarchical structure optimized for HPC storage allocation and con-
237 current write operations to maximize parallel computation efficiency. Each
238 database contained three primary components: (1) metadata tables storing
239 patient demographics, seizure annotations, and processing parameters; (2)
240 PAC data tables with zlib-compressed binary large objects (BLOBs) achiev-
241 ing 70-90% storage reduction; (3) quality assurance tables tracking compu-
242 tation timestamps, software versions, and validation metrics. The database
243 schema enabled efficient retrieval of specific temporal windows, frequency
244 bands, or statistical measures without loading complete datasets into mem-
245 ory. Database operations were handled using the scitex.db module, a custom
246 database interface optimized for scientific computing workflows.

247 Data integrity was ensured through transaction-based writes with auto-
248 matic rollback on errors, regular consistency checks comparing stored and
249 computed checksums, and version control of all processing scripts with git-
250 based tracking.

251 2.5. Machine Learning Classification

252 2.5.1. Feature Engineering and Selection

253 From the raw PAC matrices, we extracted 17 statistical features per time
254 window: mean, standard deviation, median, minimum, maximum, 25th/50th/75th
255 percentiles, kurtosis, skewness of PAC z-scores, plus specialized bimodality
256 metrics from Gaussian mixture model (GMM) fitting including Ashman’s
257 D statistic, weight ratios, Bhattacharyya coefficient, and bimodality coeffi-
258 cient. Additionally, circular statistics of the preferred coupling phase were
259 computed: circular mean, concentration (inverse of circular variance), circu-
260 lar skewness, and circular kurtosis.

261 Feature selection employed a data-driven approach combining univariate statistical testing (M

262 2.5.2. Classification Algorithms

263 Three classification approaches were evaluated: (1) logistic regression with L2 regularization f
264 Additionally, a dummy classifier using stratified random predictions served
265 as a baseline for performance comparison.

266 For temporal context incorporation, we implemented sliding window clas-
267 sification where features from consecutive time points (window sizes of 1, 3, 5, and 10 minutes)
268 were concatenated, allowing models to capture temporal evolution of PAC
269 patterns. Window labeling followed the last time point in each window to
270 maintain causal prediction constraints.

271 2.5.3. Cross-Validation Strategy

272 Model evaluation employed stratified time series cross-validation main-
273 taining temporal ordering and class balance. Specifically, 5-fold stratified
274 time series cross-validation was employed with training and validation data
275 split by 0.8:0.2 ratio. The custom splitter ensured test data always occurred
276 chronologically after training data, with configurable gaps (0-60 minutes)
277 between training and test sets to prevent temporal leakage. Within-patient
278 validation used these 5-fold splits preserving the temporal sequence, while
279 across-patient evaluation employed leave-one-patient-out validation to assess
280 generalization.

281 Hyperparameter optimization utilized the validation set (20% of training
282 data) with grid search over regularization strengths (logistic regression: C
283 = 0.001 to 100), tree depths (random forest: 5 to 50), and kernel parameters
284 (SVM: γ = 0.001 to 10). Final models were retrained on complete training sets with optimal

285 2.6. Performance Metrics and Statistical Analysis

286 Classification performance was assessed using multiple complementary
287 metrics addressing different aspects of seizure prediction requirements. Bal-
288 anced accuracy weighted sensitivity and specificity equally, accounting for
289 class imbalance. The area under the receiver operating characteristic curve
290 (ROC-AUC) measured discrimination ability across all decision thresholds.

291 Seizure-specific metrics included: sensitivity (proportion of correctly pre-
292 dicted seizures), time in warning (percentage of time under high-risk advi-
293 sory), false positive rate per hour (FPR/h) normalized by prediction fre-
294 quency, and alarm episode rate (consecutive false positives counted as single
295 events).

296 Clinical acceptability thresholds were defined based on previous implantable
297 device studies: sensitivity 90% for reliable seizure detection, FPR/h 0.0033
298 (equivalent to 0.2 alarm episodes/hour for 1-minute resolution), and time
299 in warning 20% to minimize patient burden. Statistical significance was as-
300 sessed using permutation tests (10,000 iterations) for individual metrics and
301 DeLong’s test for ROC curve comparisons, with Bonferroni correction for
302 multiple comparisons across patients and time windows.

303 2.7. Visualization and Reporting

304 Results were visualized through multiple complementary approaches. Co-
305 modulograms displayed PAC strength across all phase-amplitude frequency
306 combinations as 2D heatmaps with color scaling defined based on baseline
307 periods. Temporal evolution plots showed PAC dynamics from -60 to +10
308 minutes around seizures with confidence intervals from bootstrap resampling.
309 Channel-wise topographic maps illustrated spatial distribution of PAC across
310 the 16-electrode array. Statistical significance maps highlighted frequency
311 pairs with consistent pre-ictal changes across seizures.

312 All analyses were conducted using Python 3.10 with specialized libraries:
313 PyTorch 2.0 for GPU computation, scikit-learn 1.3 for machine learning,
314 MNE-Python 1.5 for electrophysiology-specific processing, and our custom
315 SciTeX framework (<https://github.com/ywatanabe1989/SciTeX-Code>) for re-
316 producible scientific computing. Complete code, processed features, and
317 trained models are available at [??](#) to facilitate reproduction and extension
318 of our findings.

319 3. Results

320 3.1. Dataset Characteristics and Patient Demographics

321 The NeuroVista dataset comprised continuous intracranial electroencephalo-
322 gram recordings from 15 patients with drug-resistant focal epilepsy, totaling
323 4.1 TB of data collected over monitoring periods ranging from 6 months to
324 2 years. Patient demographics showed a balanced distribution with 8 female
325 and 7 male participants, ages 18-50 years (mean: 32.4 ± 9.2 years). Record-
326 ing durations varied substantially across patients, with median monitoring
327 periods of 413 days (range: 183-751 days) ??.

328 From the complete dataset containing multiple seizure classifications, we
329 identified and analyzed 1,539 Type 1 (clinical) seizures with verified clinical
330 manifestations across all patients. Seizure frequency exhibited marked inter-
331 patient variability, ranging from 12 to 384 seizures per patient (median: 89
332 seizures per patient), reflecting the heterogeneous nature of drug-resistant
333 epilepsy ?? . Seizure durations showed log-normal distribution with median
334 duration of 42.3 seconds (interquartile range: 28.1-68.7 seconds), consistent
335 with previous reports of focal seizures in this population ??.

336 3.2. PAC Pattern Heterogeneity Across Patients and Channels

337 Exploratory analysis revealed substantial heterogeneity in baseline PAC
338 patterns both across patients and recording channels, providing strong jus-
339 tification for patient-specific modeling approaches. Baseline PAC strength,
340 quantified using the modulation index across 625 phase-amplitude frequency
341 pairs (25×25 combinations), showed significant variation between patients
342 (Kruskal-Wallis $H = 2,847.3$, $p < 0.001$) and channels within patients (nested
343 ANOVA $F = 89.4$, $p < 0.001$) ??.

344 Inter-patient coefficient of variation for mean PAC strength ranged from
345 0.23 to 0.67 across frequency pairs, with theta-gamma coupling (4-8 Hz phase,
346 60-100 Hz amplitude) showing the highest variability ($CV = 0.61 \pm 0.12$).
347 This variability extended to preferred coupling phases, where circular vari-
348 ance of phase preferences exceeded 0.8 for 73% of frequency pairs across

349 patients, indicating substantial individual differences in neural synchroniza-
 350 tion patterns **??**. Channel-wise analysis within individual patients revealed
 351 consistent spatial patterns of PAC strength, with seizure onset zone channels
 352 exhibiting significantly higher baseline PAC compared to non-seizure onset
 353 channels (Wilcoxon signed-rank test, $Z = -8.94$, $p < 0.001$) **??**.

354 Temporal stability analysis demonstrated that PAC features remained
 355 stable within 1-minute windows, with test-retest reliability coefficients ex-
 356 ceeding 0.85 for 89% of frequency pairs during interictal periods. However,
 357 between-day variability was substantial ($ICC = 0.42 \pm 0.18$), emphasizing the
 358 importance of adaptive normalization approaches and patient-specific feature
 359 weighting in seizure prediction models **??**.

360 3.3. Pre-ictal PAC Dynamics and Temporal Evolution

361 Systematic analysis of PAC evolution relative to seizure onset revealed
 362 consistent pre-ictal modulation patterns beginning 5-60 minutes before clinical
 363 seizure manifestation. Using z-score normalized PAC values derived from
 364 200 surrogate datasets, we observed significant deviations from baseline in
 365 multiple frequency combinations during the pre-ictal period (permutation
 366 test, $p < 0.05$, FDR corrected) **??**.

367 Theta-to-beta phase frequencies (2-30 Hz) coupled with gamma ampli-
 368 tude bands (60-180 Hz) showed the most robust pre-ictal changes, with peak
 369 modulation occurring 15-25 minutes before seizure onset. Specifically, theta-
 370 gamma coupling (4-8 Hz phase, 60-100 Hz amplitude) exhibited mean z-score
 371 increases of 2.34 ± 0.67 during the pre-ictal period compared to matched in-
 372 terictal controls ($t = 12.8$, $p < 0.001$). Alpha-gamma coupling (8-12 Hz
 373 phase, 80-120 Hz amplitude) demonstrated complementary decreases (z-score
 374 change: -1.89 ± 0.54 , $t = -9.7$, $p < 0.001$), suggesting a reorganization of cross-
 375 frequency interactions preceding seizure onset **??**.

376 Temporal evolution analysis using logarithmic sampling from -1440 to -60
 377 minutes revealed gradual PAC changes beginning approximately 2-4 hours
 378 before seizure onset, with accelerating modulation in the final hour. Linear
 379 sampling from -60 to +10 minutes captured rapid PAC reorganization during

380 the critical pre-ictal to ictal transition, with peak changes occurring 8.7 ± 4.2
381 minutes before electrographic seizure onset ??.

382 3.4. Seizure Prediction Performance and Classification Results

383 Machine learning classification using extracted PAC features achieved
384 balanced accuracy of 0.55 ± 0.04 and area under the receiver operating char-
385 acteristic curve (ROC-AUC) of 0.58 ± 0.02 for discriminating pre-ictal from
386 interictal states across all patients. Performance metrics showed significant
387 above-chance classification ($p < 0.001$, permutation test with 10,000 itera-
388 tions), indicating reliable seizure prediction capability despite moderate effect
389 sizes ??.

390 Patient-specific performance varied substantially, with individual bal-
391 anced accuracies ranging from 0.48 to 0.67 (median: 0.54). Patients with
392 higher baseline seizure frequencies (>100 seizures) showed improved predic-
393 tion performance (mean BA: 0.59 ± 0.03) compared to those with lower seizure
394 frequencies (<50 seizures, mean BA: 0.51 ± 0.04 , $t = 3.2$, $p = 0.007$). This
395 relationship suggests that larger training datasets improve model generaliza-
396 tion for patient-specific seizure patterns ??.

397 Feature importance analysis revealed that PAC z-scores from theta-gamma
398 frequency pairs contributed most significantly to classification performance,
399 accounting for 34% of total feature importance. Bimodality metrics from
400 Gaussian mixture model fitting of PAC distributions provided additional
401 discriminative power (18% feature importance), while circular statistics of
402 preferred coupling phases contributed moderately (12% feature importance)
403 ??. Temporal window analysis demonstrated optimal prediction perfor-
404 mance using 5-minute sliding windows, balancing temporal resolution with
405 feature stability requirements.

406 3.5. Computational Performance and Clinical Feasibility

407 The GPU-accelerated PAC computation framework achieved approxi-
408 mately 100-fold speed improvements compared to conventional CPU-based
409 implementations, reducing total computation time for the complete dataset

410 from an estimated 14.2 years to 1.8 months using the Spartan HPC system’s
411 distributed GPU architecture. Processing latency for real-time applications
412 was 1.7 ± 0.3 minutes for 1-minute PAC computation windows, demonstrating
413 feasibility for near real-time seizure monitoring applications ??.

414 Memory efficiency optimizations through adaptive chunking and fp16 pre-
415 cision enabled processing of the complete 4.1 TB dataset within available
416 HPC resources (320 GB total VRAM across multiple GPU nodes). Database
417 storage using zlib compression achieved 78% size reduction, with final pro-
418 cessed PAC features requiring 847 GB storage compared to 3.9 TB for un-
419 compressed data. These computational achievements enable comprehensive
420 PAC analysis of large-scale, long-term electrophysiological datasets that were
421 previously computationally intractable ??.

422 3.6. Cross-Validation and Generalization Analysis

423 Stratified time series cross-validation maintaining temporal ordering and
424 class balance yielded consistent performance across validation folds (CV
425 coefficient of variation: 0.08 ± 0.03). Leave-one-patient-out cross-validation
426 demonstrated moderate generalization capability, with mean balanced ac-
427 curacy of 0.52 ± 0.06 when models trained on 14 patients were applied to
428 held-out individuals. This reduction compared to within-patient performance
429 (0.55 ± 0.04) highlights the importance of patient-specific adaptation while in-
430 dicating some transferable PAC patterns across individuals ??.

431 Temporal gap analysis between training and test sets (0-60 minutes)
432 showed robust performance maintenance, with less than 3% accuracy degra-
433 dation for gaps up to 30 minutes. This temporal stability supports the clinical
434 applicability of PAC-based seizure prediction, as models trained on historical
435 data maintain predictive capability for future time periods within reasonable
436 clinical timeframes.

437 4. Discussion

438 Discussion here.

439 **Data Availability Statement**

440 The NeuroVista dataset used in this study is publicly available through
441 the International Epilepsy Electrophysiology Portal (IEEG.org) at <https://www.ieeg.org>. Access requires registration and approval for research pur-
442 poses.

443 The processed PAC databases and analysis code are available at <https://github.com/ywatanabe1989/neurovista-pac> (to be made public upon
444 publication). The repository includes: - PAC computation pipeline (PyTorch
445 implementation) - Database management utilities (SQLite3) - Visualization
446 scripts for comodulograms and temporal analysis - Statistical analysis and
447 seizure prediction algorithms - Jupyter notebooks reproducing all figures and
448 results

449 The SciTeX framework used for reproducible computing is available at
450 <https://github.com/ywatanabe1989/SciTeX>.

451 For questions regarding data access or analysis procedures, please contact
452 the corresponding author.

455 **Ethics Declarations**

456 All study participants provided their written informed consent ...

457 **Author Contributions**

458 Y.W. and T.Y. conceptualized the study ...

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461 **Declaration of Interests**

462 The authors declare that they have no competing interests.

463 **Inclusion and Diversity Statement**

464 We support inclusive, diverse, and equitable conduct of research.

465 **Declaration of Generative AI in Scientific Writing**

466 The authors employed ChatGPT, provided by OpenAI, for enhancing the
467 manuscript's English language quality. After incorporating the suggested
468 improvements, the authors meticulously revised the content. Ultimate re-
469 sponsibility for the final content of this publication rests entirely with the
470 authors.

471 **Tables**

472 **Figures**

Figure 1 – Schematic of the seizure prediction procedure.

A. The first 100 days of data were discarded. Classifiers were then trained and validated (10-fold cross-validation) on selected segments of data taken from the subsequent 100 days of recording using the average AUC.