Seizure prediction and machine learning

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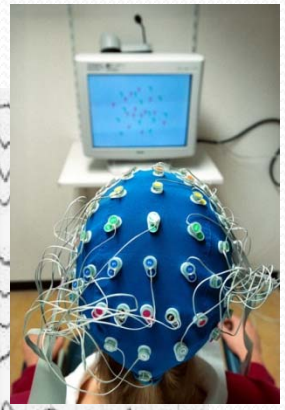
March 11, 2014

Epilepsy

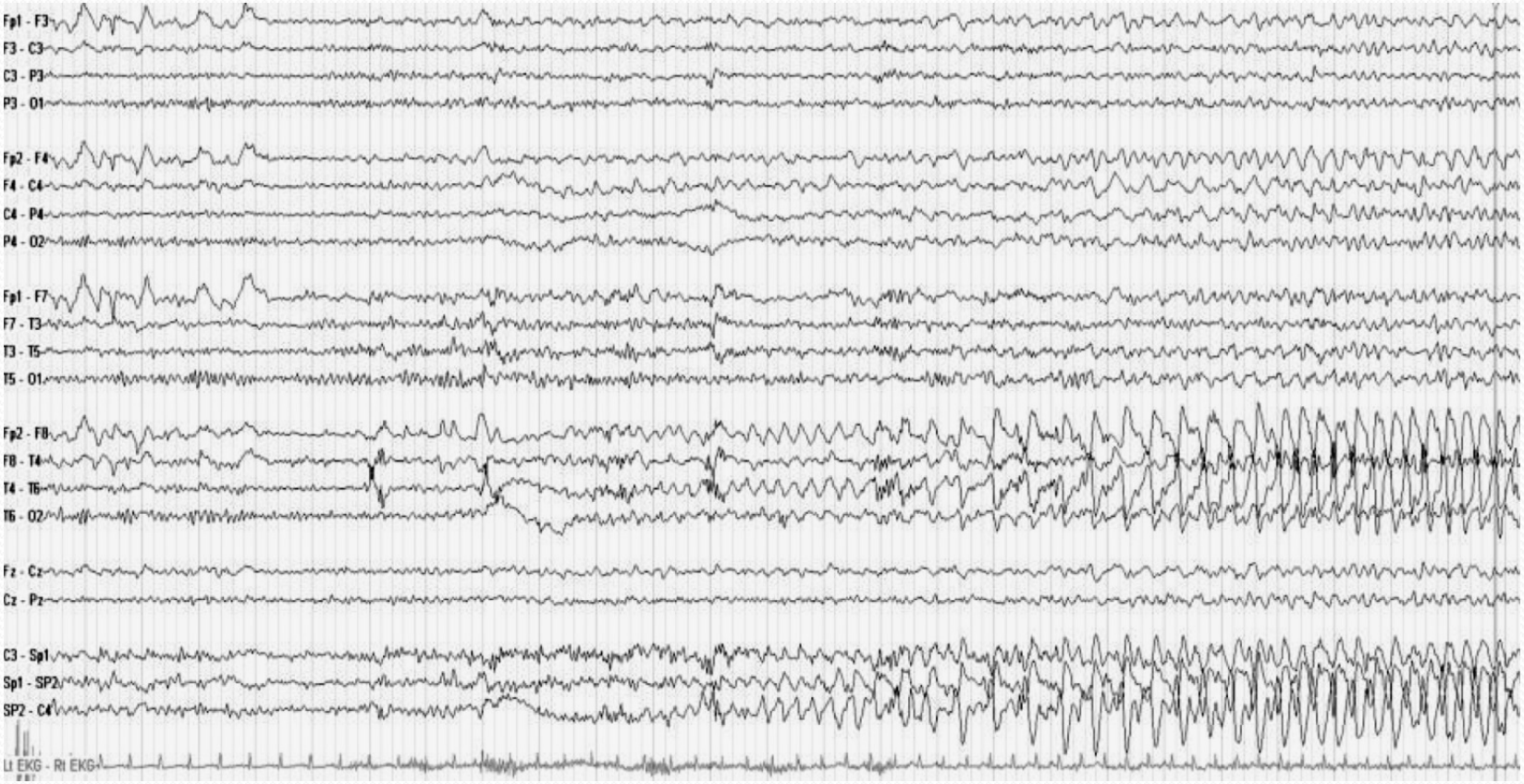
- Group of long-term neurological disorders characterized by epileptic seizures.
- Seizures involve excessive, abnormal nerve discharge in cerebral cortex.
- Wide spectrum of severity and symptoms.
  - About 60% of patients have convulsive seizures with loss of consciousness.
  - Frequency of episodes varies from several per day to a few per year.
- Underlying causes mostly obscure.
- Common disorder affecting 1% of world's population.

Electroencephalography (EEG)



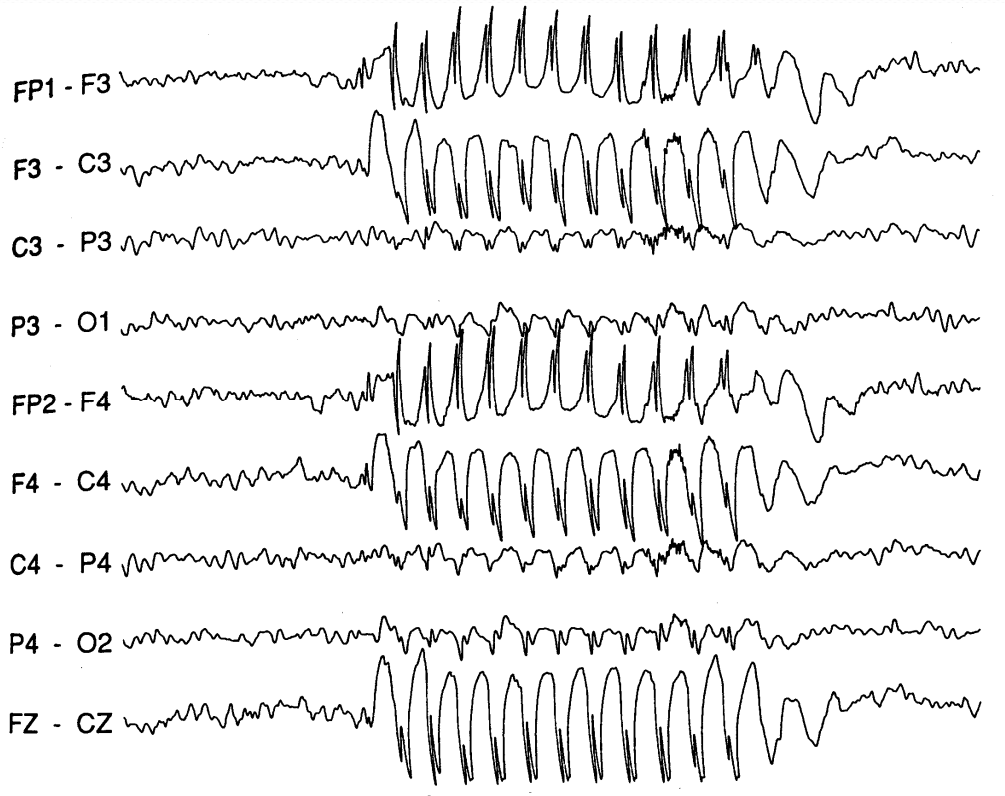
http://teddybrain.files.wordpress.com/2013/02/interictal-eeg-of-mesial-temporal-lobe-epilepsy.jpg

EEG of temporal lobe epilepsy



http://teddybrain.files.wordpress.com/2013/02/ictal-eeg-of-mesial-temporal-lobe-epilepsy.jpg

EEG of absence seizure



http://brain.fuw.edu.pl/~suffa/Modeling_SW.html

Epilepsy treatment

- Mainstay of therapy is anti-epileptic medications.
  - Medications produce significant cognitive and physical side-effects.
  - 20 - 40% of patients continue to have seizures.
  - Alternatives to medication mostly involve surgery.
- Major source of disability is anxiety over occurrence of next seizure.
  - Often leads to self-imposed, severe limitations on physical and social activities.

Seizure prediction

- Reliable prediction (forecast) of seizures would allow patients to take prophylactic medication or withdraw to a safe place.

Relative difficulty:

prediction >>> detection

- Prediction is hard.
  - Predictive signals are subtle and buried in mass of other signals.
  - Proving the predictions are statistically better than a random model is very difficult.

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COMPANY NEWS

NeuroVista and Partners to Explore New Ways to Predict and Control Seizures

NeuroVista Featured as a Promising New Epilepsy Therapy at 2012 Epilepsy Pipeline Update Conference

NeuroVista Announces Preliminary Algorithm Performance of Seizure Advisory System

NeuroVista Receives Approval for Expanding Australian Clinical Study

NeuroVista Seizure Advisory System (SAS)

Records intracranial EEG (iEEG)

- continuous
- long-term
- ambulatory

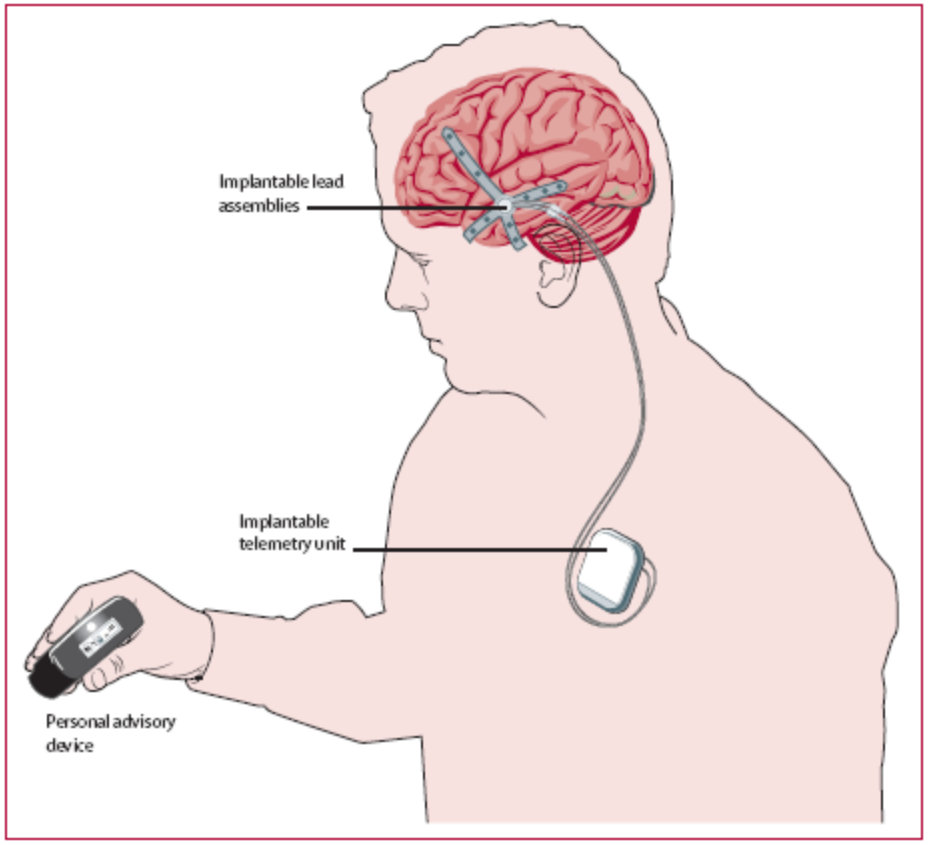

Figure 1: **Major components of seizure advisory system**
Intracranial electrode arrays (location shown by grey areas) were used to collect intracranial electroencephalogram (EEG) data on the cortical surface. Leads were connected to a subclavicularly placed implanted telemetry unit, which wirelessly transmitted data to an external, hand-held personal advisory device. The external device received the telemetered EEG, applied an algorithm to the data, and displayed the resultant information as a series of advisory lights—blue (low), white (moderate), or red (high) indicators—in addition to an audible tone or vibration, or both. The hand-held device could be worn on the belt or carried in a bag.

Output from SAS

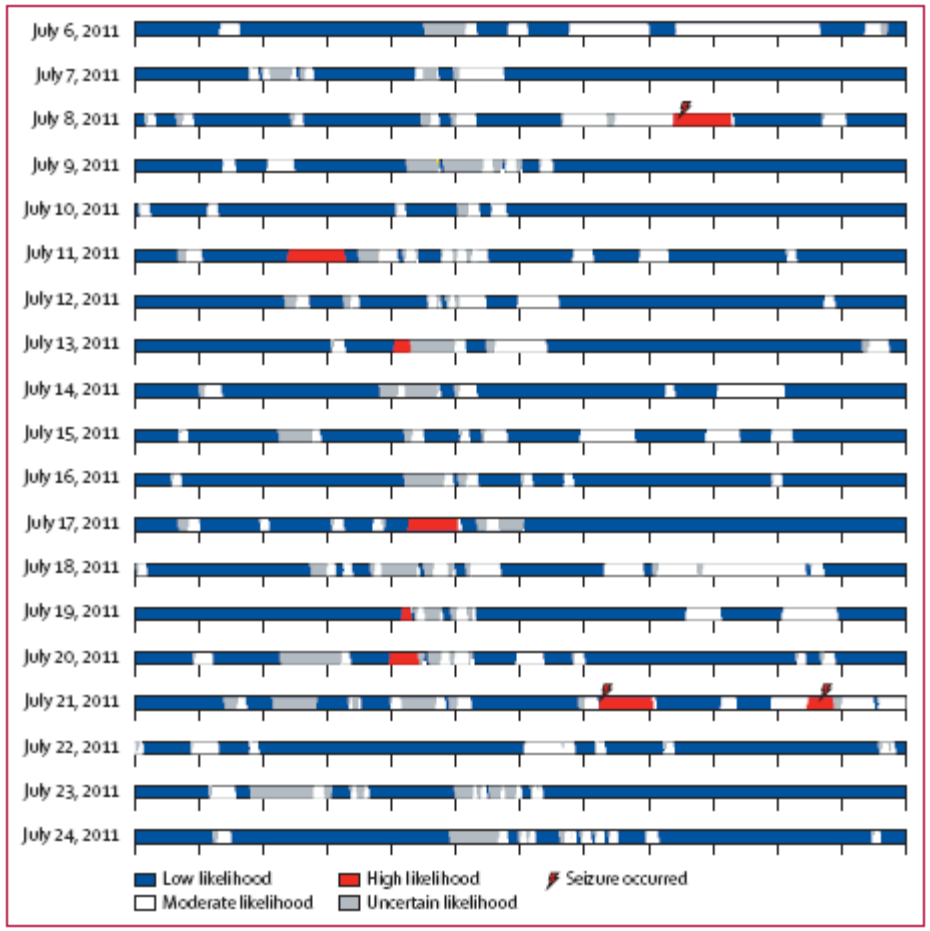

Figure 3: Excerpt from patient 2's advisory timeline
Each horizontal row represents a day broken into 2 h periods. Within each line, pixel columns are 2·3 min in duration and are broken down vertically into 13·8 s pixels. During periods of uncertain likelihood, the algorithm could not provide advisories because of data loss. From top to bottom, left to right, warning times for seizures were 14·9 min, 6·3 min, and 29·7 min.

Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study

Mark J Cook, Terence J O'Brien, Samuel F Berkovic, Michael Murphy, Andrew Morokoff, Gavin Fabinyi, Wendyl D'Souza, Raju Yerra, John Archer, Lucas Litewka, Sean Hosking, Paul Lightfoot, Vanessa Ruedebusch, W Douglas Sheffield, David Snyder, Kent Leyde, David Himes

Summary

Background Seizure prediction would be clinically useful in patients with epilepsy and could improve safety, increase independence, and allow acute treatment. We did a multicentre clinical feasibility study to assess the safety and efficacy of a long-term implanted seizure advisory system designed to predict seizure likelihood and quantify seizures in adults with drug-resistant focal seizures.

Methods We enrolled patients at three centres in Melbourne, Australia, between March 24, 2010, and June 21, 2011. Eligible patients had between two and 12 disabling partial-onset seizures per month, a lateralised epileptogenic zone, and no history of psychogenic seizures. After devices were surgically implanted, patients entered a data collection phase, during which an algorithm for identification of periods of high, moderate, and low seizure likelihood was established. If the algorithm met performance criteria (ie, sensitivity of high-likelihood warnings greater than 65% and performance better than expected through chance prediction of randomly occurring events), patients then entered an advisory phase and received information about seizure likelihood. The primary endpoint was the number of device-related adverse events at 4 months after implantation. Our secondary endpoints were algorithm performance at the end of the data collection phase, clinical effectiveness (measures of anxiety, depression, seizure severity, and quality of life) 4 months after iniation of the advisory phase, and longer-term adverse events. This trial is registered with ClinicalTrials.gov, number NCT01043406.

Findings We implanted 15 patients with the advisory system. 11 device-related adverse events were noted within four months of implantation, two of which were serious (device migration, seroma); an additional two serious adverse events occurred during the first year after implantation (device-related infection, device site reaction), but were resolved without further complication. The device met enabling criteria in 11 patients upon completion of the data collection phase, with high likelihood performance estimate sensitivities ranging from 65% to 100%. Three patients' algorithms did not meet performance criteria and one patient required device removal because of an adverse event before sufficient training data were acquired. We detected no significant changes in clinical effectiveness measures between baseline and 4 months after implantation.

Interpretation This study showed that intracranial electroencephalographic monitoring is feasible in ambulatory patients with drug-resistant epilepsy. If these findings are replicated in larger, longer studies, accurate definition of preictal electrical activity might improve understanding of seizure generation and eventually lead to new management strategies.

NeuroVista SAS in human trials

- Study phases
  - Implantation
  - Stabilization of EEG after surgery
  - Data collection
    - Minimum of 1 month and 5 lead seizures
  - Algorithm training on collected data
    - Must satisfy performance criteria under cross-validation
  - Advisory enablement
  - Advisory observation for 4 months
  - Prospective evaluation of advisory performance

NeuroVista SAS in human trials

	Data collection phase (cross-validation estimate)						Advisory phase (prospective performance at 4 months)					
	Time in advisory (%)		High likelihood performance				Time in advisory (%)		High likelihood performance			
	High	Low	Seizures (n)	Sensitivity (%)	p	Phase duration (days)	High	Low	Seizures (n)	Sensitivity	p	Likelihood ratio
Patient 1	33	27	8 (16)	75%	0·0142 (0·00	95·8	27	7	7 (13)	86% (77%)	0·0017	14·3
Patient 2	21	58	4	75%	0·02	31	56		3	100%	0·0266	All*
Patient 3	42	Not enabled	37 (45)	65% (64%)	0·00 (0·0013)			enabled			(0·0001)	
Patient 4†	15	46	8 (9)	71% (75%)	0·0009 (0·0002)	183·8	..	..	..	..	..	..
Patient 8	40	Not enabled	29 (65)	69% (63%)	0·0010 (0·0001)	143·0	28	Not enabled	36 (86)	63% (62%)	0·0003 (<0·0001)	4·4 (4·2)
Patient 9	36	19	15 (17)	67% (59%)	0·0120 (0·0401)	153·9	11	48‡	49 (52)	18%§ (17%)	0·0839 (0·1419)	0·8
Patient 10	31	Not enabled	14 (20)	71% (75%)	0·0013 (<0·0001)	142·7	17	Not enabled	109 (164)	54% (51%)	<0·0001	5·8 (5·1)
Patient 11	30	20	20 (74)	93% (65%)	<0·0001	90·7	15	26	11 (39)	56% (39%)	0·0039 (0·0003)	5·1 (2·6)
Patient 13	35	Not enabled	17 (44)	73% (62%)	0·0021 (0·00	149·9	28	Not	26 (113)	57% (50%)	0·0021	3·4 (5·1)
Patient 14	5	83	5 (6)	100%	<0·00	3	88		3	100%	<0·0001	All*
Patient 15	18	Not enabled	5 (6)	100%	0·0002 (<0·0001)	157·5	41	Not enabled	21 (24)	71%	0·0034 (0·0019)	3·6 (3·5)

Performance data were assessed on the basis of correlated clinical seizures. Patients 5, 6, 7, and 12 did not proceed to the advisory phase, either because an adverse event led to device removal despite satisfactory preliminary data acquisition (patient 5), or because the algorithm generated on completion of the data collection phase did not meet the predetermined performance criteria (patients 6, 7, and 12). Assessments based on the use of clinical equivalent seizures in addition to correlated clinical seizures are provided in parentheses, when different. Likelihood ratio=([number of events in high advisory]/[time in high advisory])/([number of events in moderate advisory]/[time in moderate advisory]). *All events occurred during the high likelihood advisory. †Patient discontinued study because of adverse events before the 4 month advisory endpoint. ‡Negative predictive value <100%; all other low likelihood advisories had a negative predictive value of 100%. §Performance criteria were not satisfied prospectively.

Table 3: Algorithm performance, by patient

NeuroVista SAS in human trials

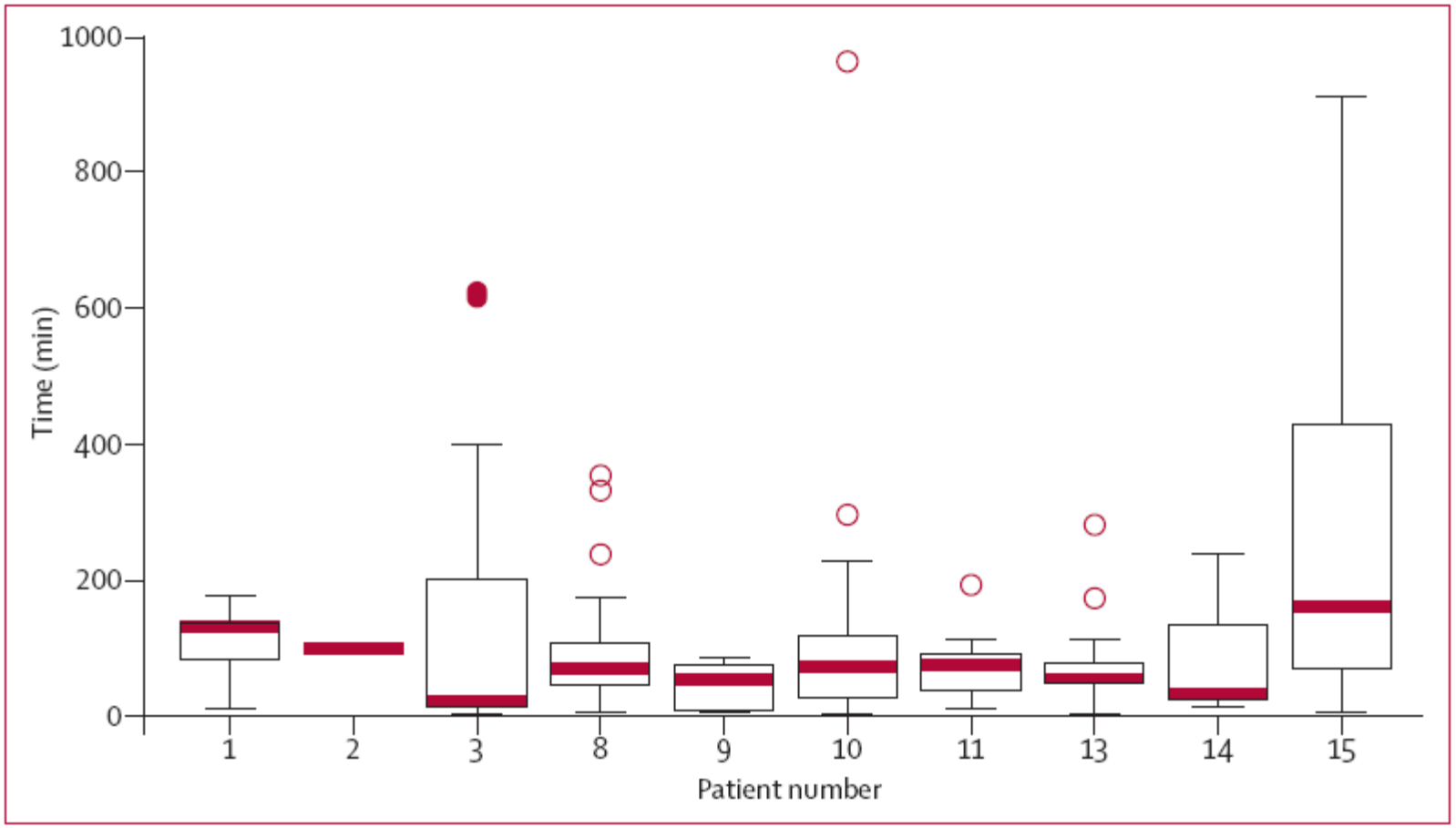

***Figure 2*: Box plots of time between start of the red advisory and seizures, by patient**
Solid lines represent medians, top whiskers maxima, bottom whiskers minima, box tops 75th percentiles, box bottoms 25th percentiles, and circles outliers.

Classification definition

- Given a collection of records (*training set*)
  - Each record contains a set of *features*.
  - Each record also has a discrete *class label*.
- Learn a *model* that predicts class label as a function of the values of the features.
- Goal: model should assign class labels to previously unseen records as accurately as possible.
  - A *test set* is used to determine the accuracy of the model. Usually, the given data set is divided into training and test sets, with training set used to build the model and test set used to validate it.

Classification illustrated

categorical | categorical | continuous | class

Tid	Refund	Marital Status	Taxable Income	Cheat
1	Yes	Single	125K	No
2	No	Married	100K	No
3	No	Single	70K	No
4	Yes	Married	120K	No
5	No	Divorced	95K	Yes
6	No	Married	60K	No
7	Yes	Divorced	220K	No
8	No	Single	85K	Yes
9	No	Married	75K	No
10	No	Single	90K	Yes

Training set

Learn classifier

Model

Refund	Marital Status	Taxable Income	Cheat
No	Single	75K	?
Yes	Married	50K	?
No	Married	150K	?
Yes	Divorced	90K	?
No	Single	40K	?
No	Married	80K	?

Test set

Predicted classes

NeuroVista predictive algorithms

	First generation	Second generation
Features	spectral power based, somewhat complex	??
Feature resolution	one second	??
Discriminant function	complex, non-linear	??
iEEG recordings used for development	short-term human	??
Human trials	effective	??

NeuroVista predictive algorithms

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Features	spectral power based, somewhat complex	??
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Discriminant function	complex, non-linear	??
iEEG recordings used for development	short-term human	??
Human trials	effective	??

NeuroVista predictive algorithms

	First generation	Second generation
Features	spectral power based, somewhat complex	spectral power based, simplified
Feature resolution	one second	one minute
Discriminant function	complex, non-linear	logistic regression
iEEG recordings used for development	short-term human	long-term canine
Human trials	effective	untested

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PLOS ONE

Forecasting Seizures in Dogs with Naturally Occurring Epilepsy

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Abstract

Seizure forecasting has the potential to create new therapeutic strategies for epilepsy, such as providing patient warnings and delivering preemptive therapy. Progress on seizure forecasting, however, has been hindered by lack of sufficient data to rigorously evaluate the hypothesis that seizures are preceded by physiological changes, and are not simply random events. We investigated seizure forecasting in three dogs with naturally occurring focal epilepsy implanted with a device recording continuous intracranial EEG (iEEG). The iEEG spectral power in six frequency bands: delta (0.1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), low-gamma (30–70 Hz), and high-gamma (70–180 Hz), were used as features. Logistic regression classifiers were trained to discriminate labeled pre-ictal and inter-ictal data segments using combinations of the band spectral power features. Performance was assessed on separate test data sets via 10-fold cross-validation. A total of 125 spontaneous seizures were detected in continuous iEEG recordings spanning 6.5 to 15 months from 3 dogs. When considering all seizures, the seizure forecasting algorithm performed significantly better than a Poisson-model chance predictor constrained to have the same time in warning for all 3 dogs over a range of total warning times. Seizure clusters were observed in all 3 dogs, and when the effect of seizure clusters was decreased by considering the subset of seizures separated by at least 4 hours, the forecasting performance remained better than chance for a subset of algorithm parameters. These results demonstrate that seizures in canine epilepsy are not randomly occurring events, and highlight the feasibility of long-term seizure forecasting using iEEG monitoring.

Canine subjects

Specifics of iEEG records for three canines with naturally occurring epilepsy implanted with the NeuroVista Seizure Advisory System.

Subject ID (Breed)	MRI Brain	Recording duration, days	Number all seizures	Number lead seizures
002 Mixed	Normal	197 *	27	27
004 Mixed	Normal	330	15	8
007 Mixed	Normal	451	83	18
Group totals (mean ± std)		978 (326 ± 127)	125 (41.7 ± 36.3)	53 (17.7 ± 9.5)

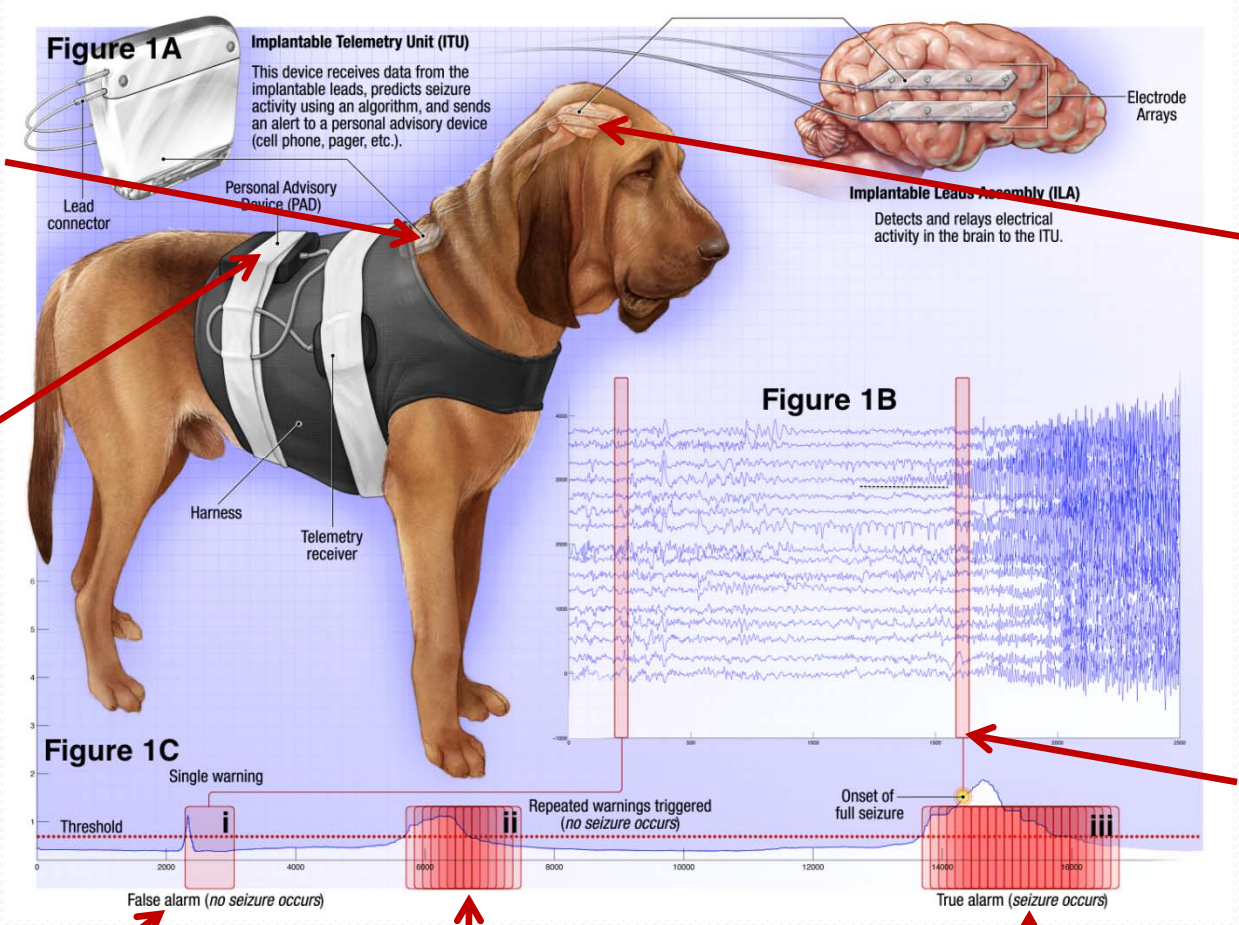
Lead seizures were defined as seizures preceded by at least 4 hours of non-seizure.

* Full record was 475 days in duration; only final 197 days used for forecasting to avoid post-surgical non-stationarities in iEEG.

Seizure Advisory System in canines

Implantable Telemetry Unit

Personal Advisory Device



Implantable Leads Assembly

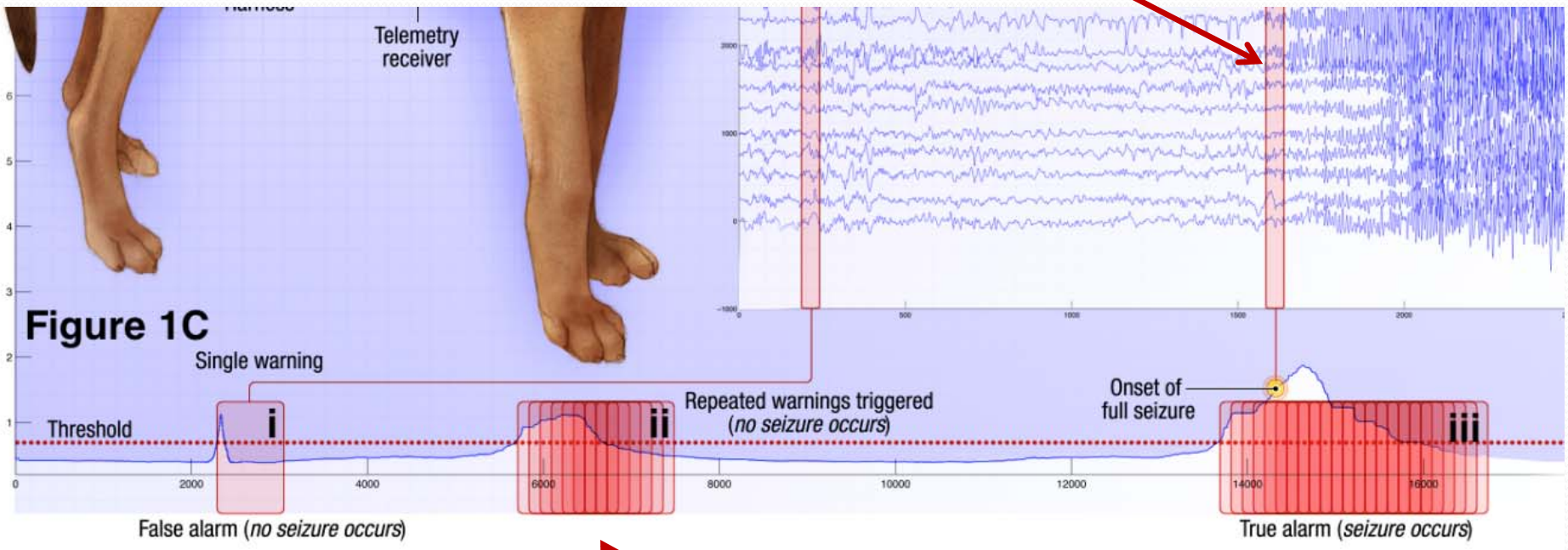
onset of full seizure

single warning triggered
no seizure
(false positive)

repeated warnings triggered
no seizure
(false positive)

repeated warnings triggered
seizure occurs
(true positive)

Seizure Advisory System in canines

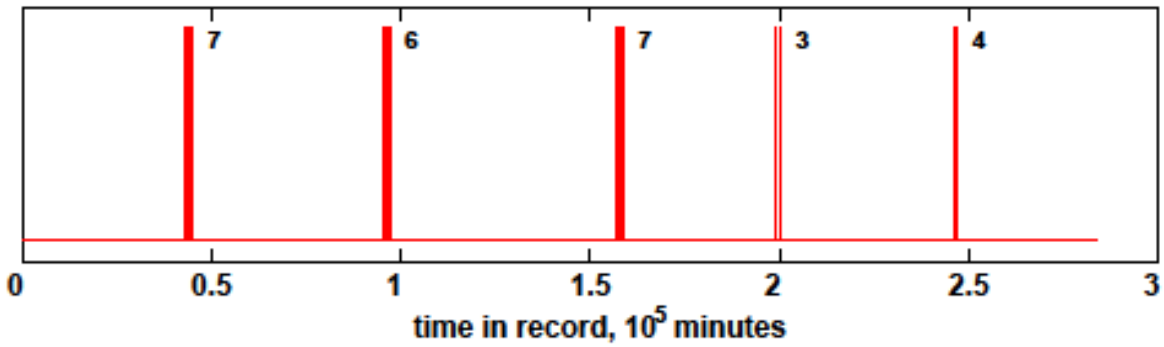


single warning triggered
no seizure
(false positive)

repeated warnings triggered
no seizure
(false positive)

repeated warnings triggered
seizure occurs
(true positive)

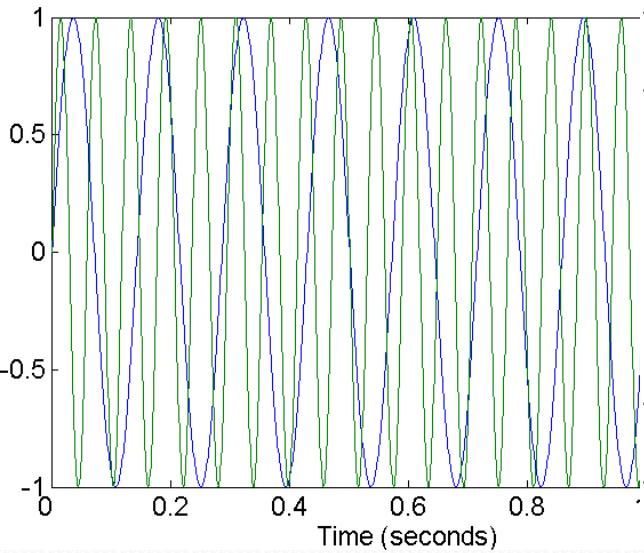
Full seizure record, canine subject 002



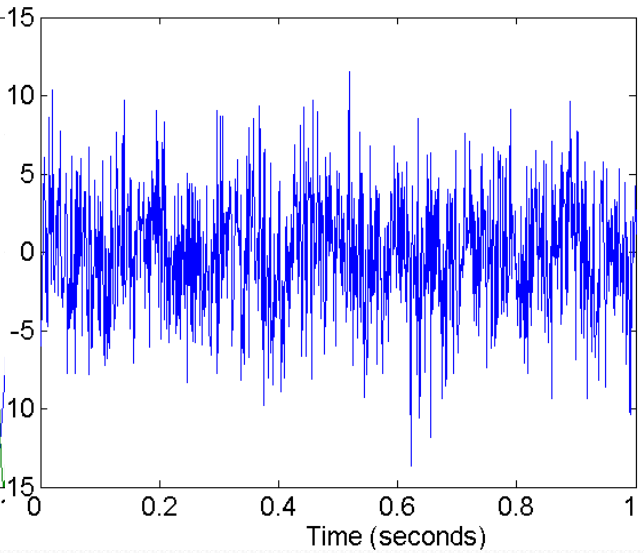
197 days

Fourier transform

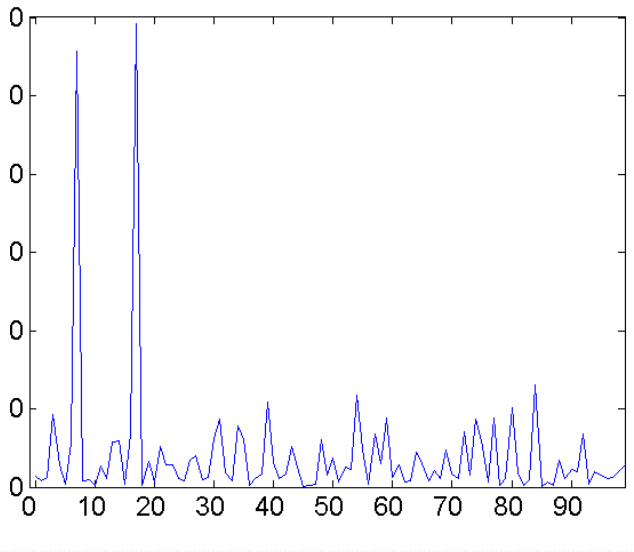
transform data from time domain to frequency domain



two sine waves



two sine waves + noise



frequency

Extraction of power bands from iEEG

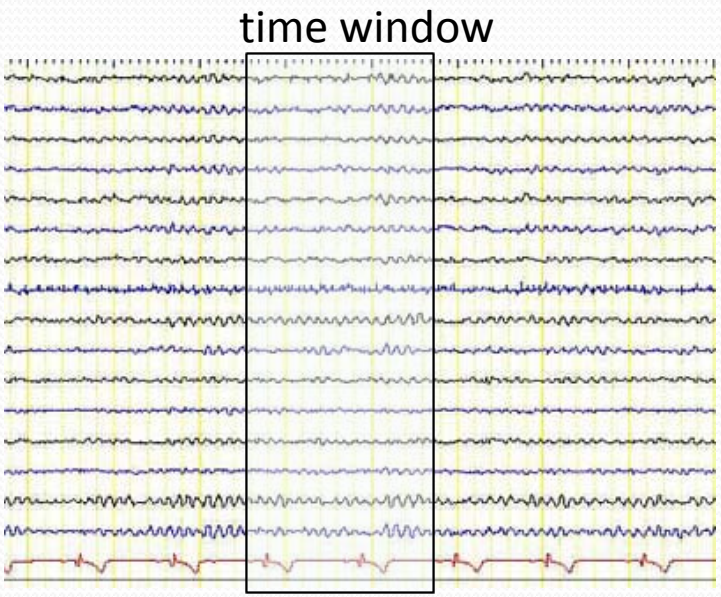
1) For each one-minute time interval (24000 samples of raw iEEG):
   - Fourier transform on each of 16 channel EEG to give corresponding channel power spectrum (16384 frequencies)
2) For whole record:
   - Normalize power at each frequency in each channel
3) For each one-minute time interval:
   - Segment power spectrum into bands

delta	(0.1-4 Hz)	beta	(12-30 Hz)
theta	(4-8 Hz)	gamma-low	(30-70 Hz)
alpha	(8-12 Hz)	gamma-high	(70-180 Hz)

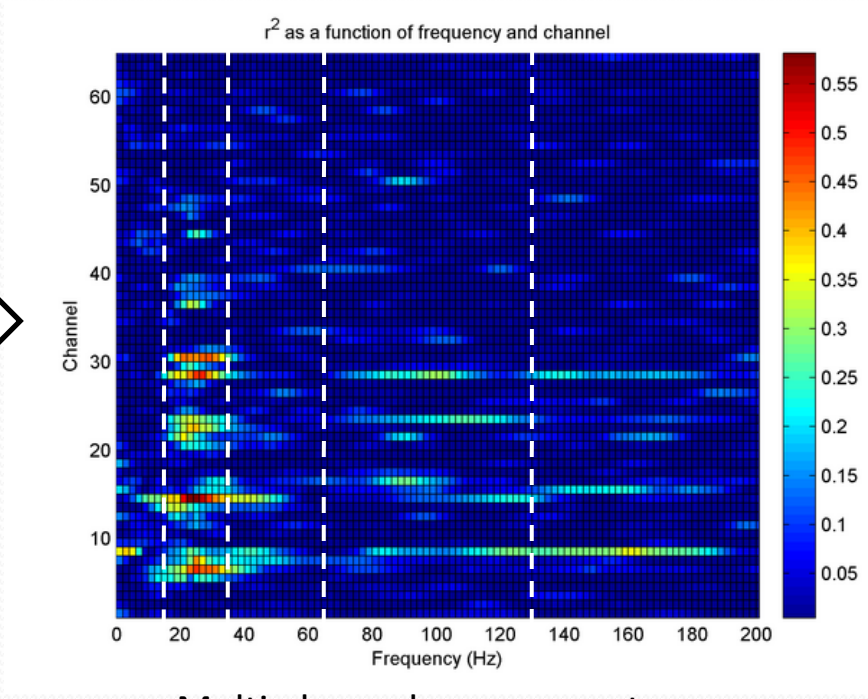
   - Create channel-band features by summing values in each band

Output: 96 *power-in-band* features with temporal resolution of one minute

Extraction of power bands from iEEG



Multi-channel iEEG recording
(time domain)



Multi-channel power spectrum
(frequency domain)

Terminology

ictal

- period of time during a seizure

preictal

- period preceding a seizure

postictal

- period following a seizure

interictal

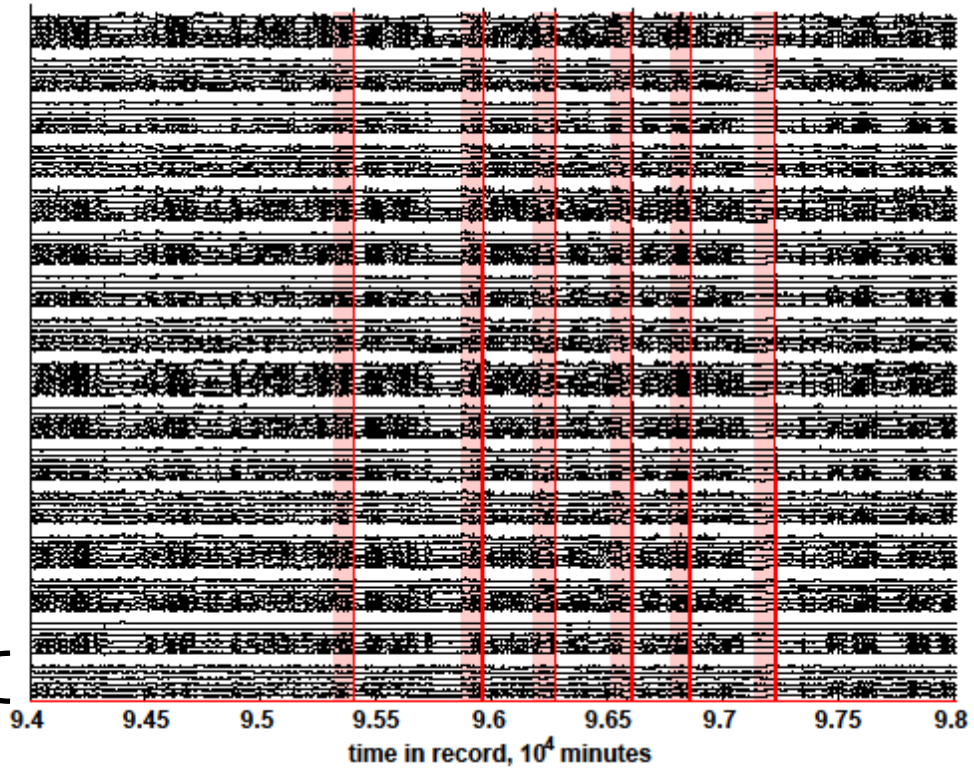
- time between seizures (neither ictal nor preictal)

Initial search for predictive algorithm

- Set up as standard two-label classification problem
- Each one-minute interval labeled as:
  - *preictal* if within 90 min. preceding a seizure
  - *interictal* otherwise
- 10-fold cross-validation with block folds
- Interictal labels much more abundant than preictal labels
  - class imbalance problem
  - address by subsampling interictal labels so have same number as preictal labels in training set
- Standard classification algorithms
  - logistic regression, neural networks, SVMs, others

Power-in-band features

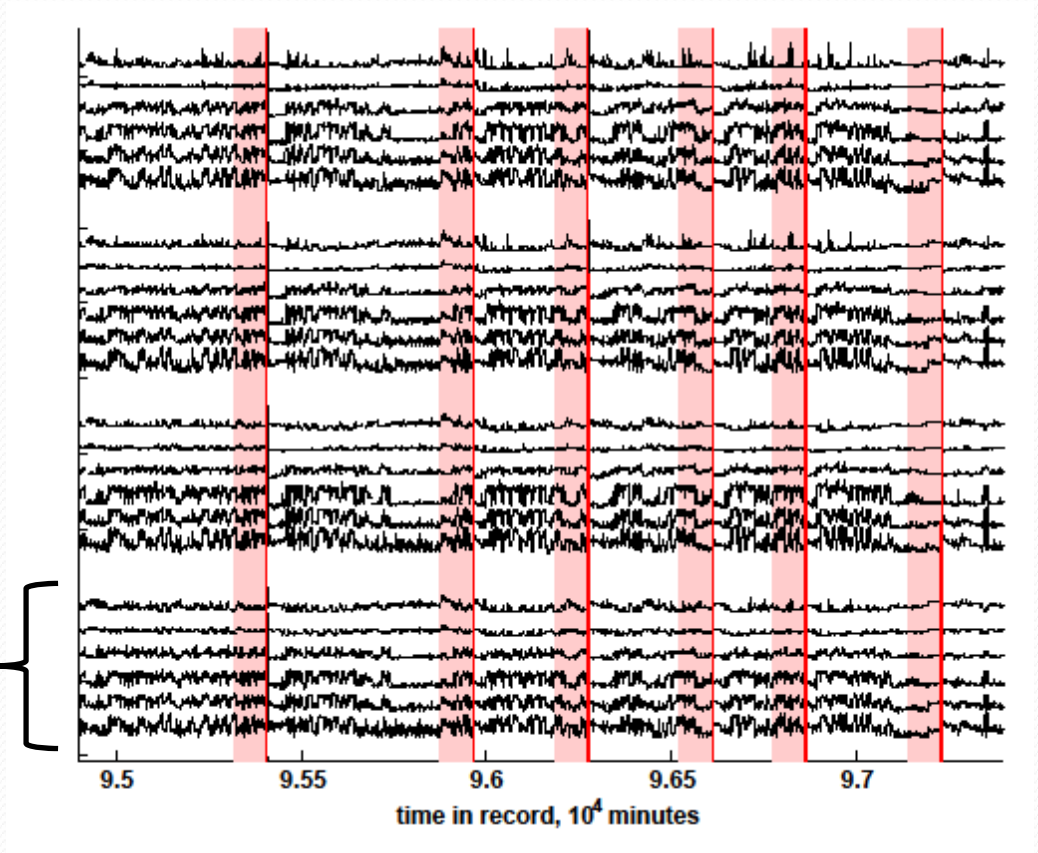
- Canine subject 002
- Time interval around seizure cluster 2
- 96 features (black)
- 6 seizures (red)
- 90 minute preictal horizon (pink shading)



6 features for channel 1

Power-in-band features

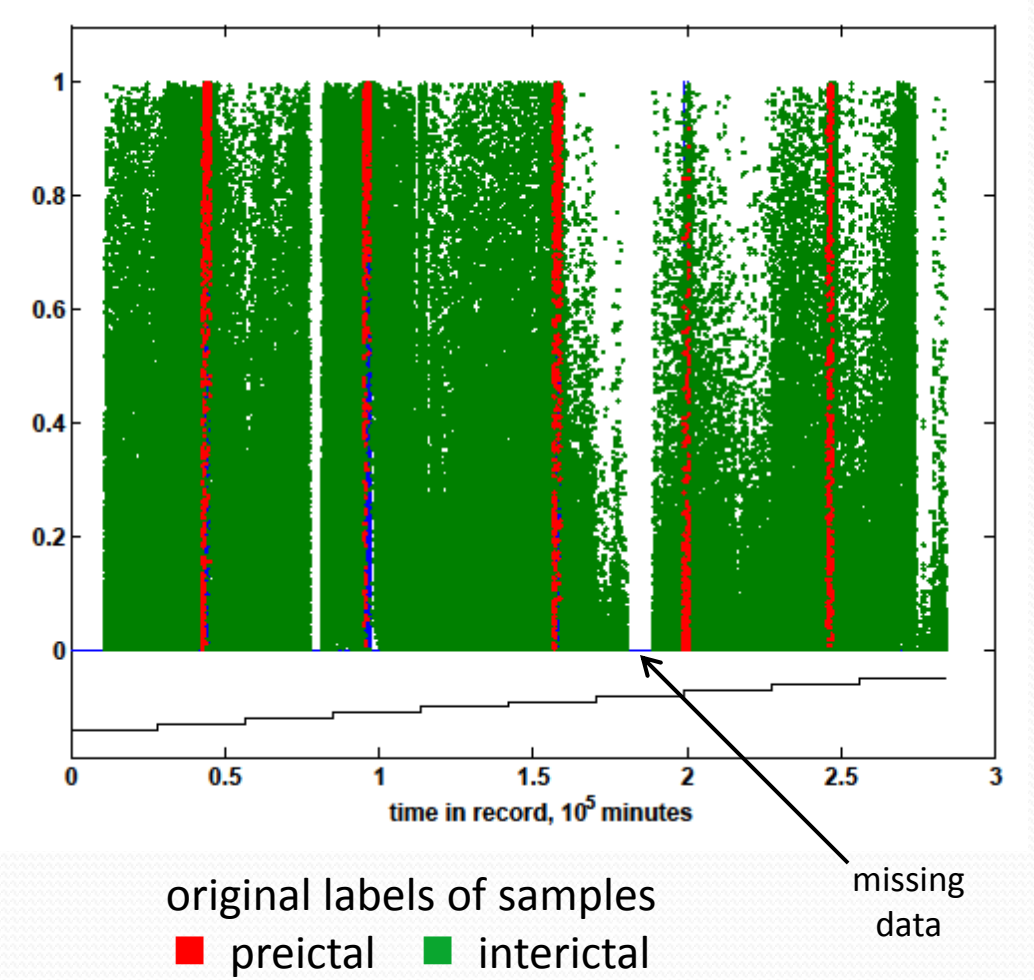
- Canine subject 002
- Seizure cluster 2
- Expansion of features for channels 9-12



Classification of preictal vs. interictal

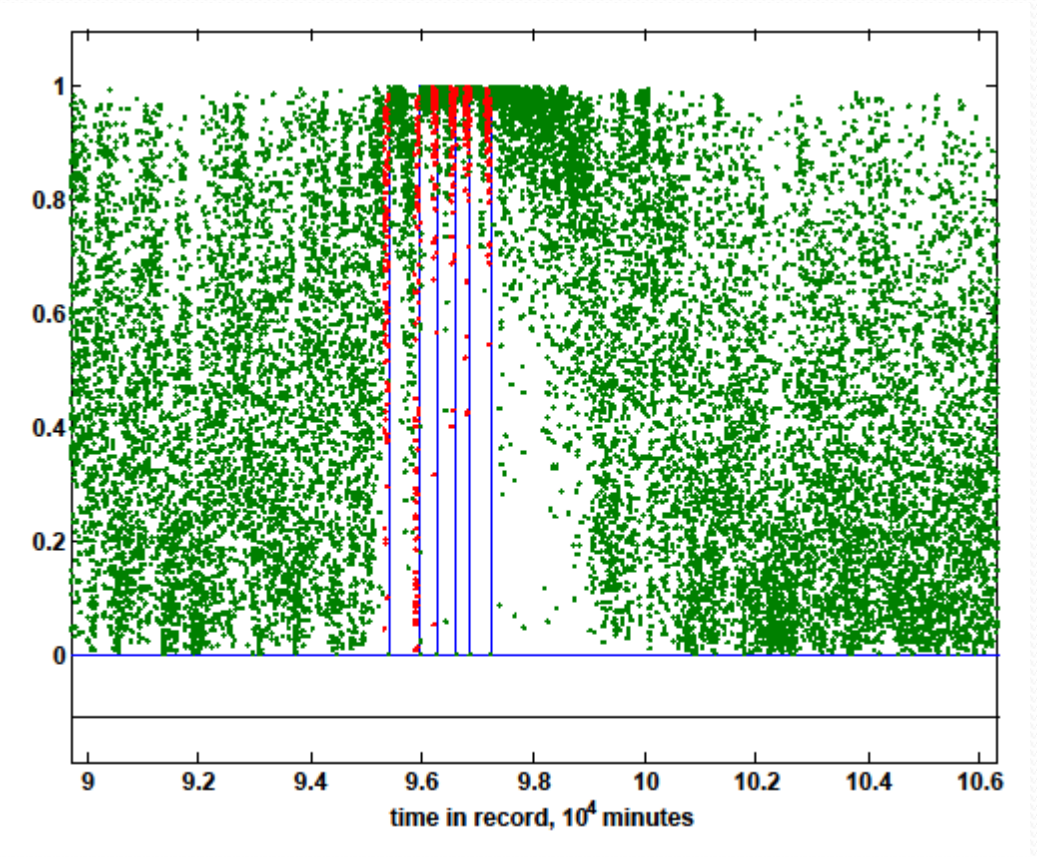
- Canine subject 002
- Full record shown
- Logistic regression
- Trained on all 96 features
- Output probability of preictal in range 0.0 - 1.0

- AUC-ROC = 0.826



Classification of preictal vs. interictal

- Canine subject 002
- Seizure cluster 2 shown



Predictive algorithm in advisory setting

- Must choose advisory threshold
  - When output of classifier exceeds threshold, warning is triggered.
  - Warning has preset persistence interval (90 min.).
  - New threshold crossing during ongoing warning extends warning.
- True positive:
  - Warning begins at least 5 min. prior to seizure.
  - Warning still in effect at time of seizure.
- False positive:
  - Warning does not overlap a seizure.

Predictive algorithm in advisory setting

- Performance evaluated within a ‘stack’ of calculations
  - Feature selection
  - Classifier training
  - Over sequence of thresholds selected to produce various targeted total time in warning (TIW):
    - Generate advisories from trained classifier
    - Generate advisories from chance predictor matched for TIW
  - Compute statistics comparing performance of trained and chance predictors
- 10-fold cross validation applied to entire stack

Chance predictor

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The statistics of a practical seizure warning system

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Abstract

Statistical methods for evaluating seizure prediction algorithms are controversial and a primary barrier to realizing clinical applications. Experts agree that these algorithms must, at a minimum, perform better than chance, but the proper method for comparing to chance is in debate. We derive a statistical framework for this comparison, the expected performance of a chance predictor according to a predefined scoring rule, which is in turn used as the control in a hypothesis test. We verify the expected performance of chance prediction using Monte Carlo simulations that generate random, simulated seizure warnings of variable duration. We propose a new test metric, the difference between algorithm and chance sensitivities given a constraint on proportion of time spent in warning, and use a simple spectral power-based measure to demonstrate the utility of the metric in four patients undergoing intracranial EEG monitoring during evaluation for epilepsy surgery. The methods are broadly applicable to other scoring rules. We present them as an advance in the statistical evaluation of a practical seizure advisory system.

Chance predictor

- Warning triggers generated randomly using a Poisson process
- Warning intervals otherwise identical to trained predictor
  - Persistence
  - Extension
  - Rules for true and false positives
- Poisson rate parameter adjusted to produce target time in warning

Advisory performance in canines

- 10 of 96 PIB features (forward selection)
- 10-fold cross-validation
- **TIW**: total time in warning
- **S_n**: sensitivity
- **p**: p-value
- **lead**: lead seizures only

ID	TIW	S_n	*p*	$S_{n\text{-lead}}$	$p_{n\text{-lead}}$	False Positive/day
002	0.1	0.482	**0.0000**	0.482	**0.0000**	1.293
002	0.15	0.593	**0.0000**	0.593	**0.0000**	1.818
002	0.2	0.667	**0.0000**	0.667	**0.0000**	2.257
002	0.3	0.741	**0.0000**	0.741	**0.0000**	2.792
002	0.35	0.741	**0.0001**	0.741	**0.0001**	2.910
002	0.4	0.889	**0.0000**	0.889	**0.0000**	3.074
002	0.5	0.889	**0.0001**	0.889	**0.0001**	3.186
004	0.1	0.000	0.2435	0.000	0.6081	0.811
004	0.15	0.133	1.0000	0.125	1.0000	0.794
004	0.2	0.467	**0.0141**	0.250	1.0000	1.079
004	0.3	0.733	**0.0007**	0.500	0.2534	1.954
004	0.35	0.733	**0.0035**	0.500	0.4691	2.335
004	0.4	0.733	**0.0183**	0.500	0.7290	2.670
004	0.5	0.800	0.0700	0.625	0.7407	3.026
007	0.1	0.759	**0.0000**	0.222	0.7548	0.658
007	0.15	0.819	**0.0000**	0.278	0.5582	0.791
007	0.2	0.843	**0.0000**	0.389	0.1658	0.991
007	0.3	0.892	**0.0000**	0.556	**0.0421**	1.427
007	0.35	0.892	**0.0000**	0.556	0.0895	1.617
007	0.4	0.904	**0.0000**	0.556	0.2270	1.695
007	0.5	0.916	**0.0000**	0.611	0.2459	1.927

NeuroVista predictive algorithms

	First generation	Second generation
Features	spectral power based, somewhat complex	spectral power based, simplified
Feature resolution	one second	one minute
Discriminant function	complex, non-linear	logistic regression
iEEG recordings used for development	short-term human	long-term canine
Human trials	effective	untested

Closing thoughts

- Caveats
  - Some of predictive performance coming from postictal signature
  - Need high sensitivity at lower total time in warning (≤ 0.1)
- Future work
  - Explore other types of features from iEEG
    - High-frequency oscillations
    - Spectral entropy
    - ???
  - Vary preictal horizon