Epileptic seizure prediction from EEG

Piotr Mirowski, Deepak Madhavan, Yann LeCun, Ruben Kuzniecky
Outline

- Seizure prediction problem, approaches
- International Seizure Prediction Group:
  - actors
  - dataset (clinical facts, preprocessing)
  - goals
- How to ensure seizure predictability?
  - ROC, sensitivity, specificity
  - Statistical: Seizure Time Surrogates
  - Algorithmic: training vs. testing dataset
- Linear univariate techniques
  - (Accumulated) energy [Esteller, Harrison]
- Linear bivariate techniques
  - Fitting autoregressive model [Jouny]
  - Cross-correlation [Mormann]
- Non-linear bivariate techniques
  - Non-linear systems
  - Dynamical entrainment [Iasemidis]
  - Nonlinear interdependence [Arnhold]
  - Phase locking
  - Phase synchronization [Le Van Quyen]
- Our research: classification of bivariate dynamical patterns
ElectroEncephaloGraphy (EEG)

Scalp EEG

Figure 1.3: Origin of scalp potentials; Current in the EEG measuring circuit depends on the nature and location of the current sources, on the electrical properties of the brain, skull and scalp and on location of both electrodes. Modified from Nunez (1981)[19].

[Suffczynski, 2000, wikipedia.org]
Intra(cranial/cerebral) EEG

[EEG database at Albert-Ludwigs-Universität in Freiburg, Germany]
Random facts about epilepsy

Epilepsy
Chronic illness
Affects 1% to 2% of world population
40% of patients refractory to medication
Resective surgery as a treatment

Partial ("focal")
Impairment of consciousness or perception
Sometimes aura for other seizures

Generalized: Absence ("petit mal")
Impairment of consciousness
Abrupt start and termination, short duration
Unpredictable (?)

-3 Hz SW

Generalized: Tonic-clonic ("grand mal")
Rhythmic muscle contractions
Loss of consciousness

Seizure prediction problem

Observation window

Seizure onset

intracranial EEG (numerical data)

Extraction of **features** from EEG channels,
**pattern** recognition, ...
+ classification

prediction horizon

[Litt and Echauz, 2002]
Overview

The RNS™ System, designed for the treatment of medically refractory partial epilepsy, includes implantable and external products.

Implantable components include the RNS neurostimulator as well as depth and cortical strip leads. The RNS neurostimulator is a programmable, battery-powered, microprocessor-controlled device that delivers a short train of electrical pulses to the brain through implanted leads. In treating epilepsy, the RNS neurostimulator is designed to detect abnormal electrical activity in the brain and respond by delivering electrical stimulation to normalize brain activity before the patient experiences seizure symptoms. The neurostimulator is implanted in the cranium and connected to one or two leads that are implanted near the patient's seizure focus.

External products include the programmer, a laptop computer with proprietary software that has a wand and telemetry interface enabling communication with an implanted RNS neurostimulator. Physicians use the programmer to non-invasively program the detection and stimulation parameters of an implanted device. Additional features of the programmer include the ability to view the patient’s electrocorticographic (ECoG) activity real-time and the ability to upload the patient’s ECoGs that have been stored in the RNS neurostimulator.

Caution: The RNS™ System is an investigational device. Limited by United States law to investigational use.
## Approaches to the problem

<table>
<thead>
<tr>
<th>Feature extraction from EEG:</th>
<th>Relationship between EEG channels:</th>
<th>Classification based on:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Linear</strong></td>
<td><strong>Univariate</strong></td>
<td><strong>Statistics</strong></td>
</tr>
<tr>
<td>System of noise-driven linear equations $y(t) = ax(t) + b + \eta(t)$</td>
<td>1 channel at a time</td>
<td>Discriminating measure</td>
</tr>
<tr>
<td><strong>Non-linear</strong></td>
<td><strong>Bivariate</strong></td>
<td><strong>Algorithm</strong></td>
</tr>
<tr>
<td>Deterministic dynamical system of nonlinear equations</td>
<td>Varying synchronization of EEG channels</td>
<td>Machine Learning: neural networks, genetic optimization...</td>
</tr>
</tbody>
</table>

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Main research groups (after 2002)

International Seizure Prediction Group
Bonn, 2002

Harrison
Flint Hills Scientific (Kansas)
Energy
Statistical

Lopes da Silva, Suffczynski
SEIN Netherlands, Warsaw
Models of epilepsy

Chernihovskyi, Lehnertz
Bonn
Synchrony from Cellular NN
Algorithmic

Mormann, Andrzejak, Lehnertz
Bonn
Various features
Statistical

Journy, Franaszczuk
John Hopkins
Univariate complexity, linear synchrony
Statistical

Iasemidis, Chaovarlitwongse
Arizona State, Florida
Dynamical entrainment
Statistical

Jerger, Sauer
George Mason (Virginia)
Covariance, synchrony (Simple) algorithmic

Le Van Quyen, Navarro, Varela
Pitié-Salpêtrière (Paris)
Wavelet synchrony, dynamic similarity
Statistical

Litt, Echauz, Esteller
UPenn, GA Tech, Neuropace
Energy
Statistical/Algorithmic
ISPG Bonn 2002 dataset

<table>
<thead>
<tr>
<th>Data set</th>
<th>Sampling rate (Hz)</th>
<th>A to D conversion</th>
<th>BandPass (Hz)</th>
<th># Channels</th>
<th>#Seizures</th>
<th>ISI (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>480</td>
<td>16 bits</td>
<td>0.16-70</td>
<td>32</td>
<td>3</td>
<td>13.9 ± 13.7</td>
</tr>
<tr>
<td>Bonn</td>
<td>200</td>
<td>16 bits</td>
<td>0.30–70</td>
<td>48</td>
<td>10</td>
<td>5.9 ± 4.8</td>
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<tr>
<td>Florida</td>
<td>200</td>
<td>10 bits</td>
<td>0.10–70</td>
<td>32</td>
<td>15</td>
<td>3.9 ± 3.5</td>
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<tr>
<td>Kansas</td>
<td>239.75</td>
<td>10 bits</td>
<td>0.10–100</td>
<td>53</td>
<td>6</td>
<td>8.1 ± 6.0</td>
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<tr>
<td>UPenn</td>
<td>200</td>
<td>12 bits</td>
<td>0.50–70</td>
<td>81</td>
<td>17</td>
<td>3.6 ± 3.0</td>
</tr>
</tbody>
</table>

Continuous video+EEG recordings

Temporal lobe epilepsy, ages 18-65
Seizure-free after surgery
Sleep-wake data not provided (yet useful)
ISPG Bonn 2002 goals

Discriminate (binary classification)

Focal epilepsies (not generalized)

Premonitory symptoms in 6% of 500 patients

Seizure onset
EEG
Clinical

Earliest Unequivocal
Earliest Unequivocal

Data requirement:
4h between seizures

Observation window

Pre-ictal
Interictal
Post-ictal
Ictal
Ignored

[Lehnertz and Litt, 2005], [Litt and Echauz, 2002]
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Receiver-Operator Characteristic

Area under ROC curve

Hypothesis: \( \downarrow \) pre-ictal decrease

- **TP** true positive seizure, >1 alarm(s)
- **FP** false positive alarm, no seizure
- **TN** during prediction horizon

\[
\text{sensitivity} = \frac{TP}{TP + FN} \\
\text{specificity} = \frac{TN}{TN + FP}
\]

False prediction rate = FP/interictal time

Shorter prediction horizons = less waiting (wasted) time

[Lehnertz et al, 2007], [Mormann et al, 2006]
Statistical validation

Sub-clinical events → Same number as real seizure times

Random generation of Seizure Time Surrogates → Same number as real seizure times
→ Same distribution of intervals between seizures
→ Occurring in the same time-frame as real seizures

Null hypothesis: “no pre-ictal state [can be found]”
given a particular tested set of discriminating measures...

How to disprove it? Same EEG Same measures Ignore seizure times

[Andrzejak et al, 2003]
Statistical validation

events

'measure' from EEG

sub-clinical events

hyper-ventilation

seizure times

pre-ictal states

time (days)

- decision boundary $F$

- e.g. $F=\text{average over all channels}$

Compare 1 original vs. 19 surrogates

$F$ (original) falls into same distribution as $F$ (surrogates)

measure = Failure
Machine Learning

Training dataset “in-sample”

\[
\begin{align*}
X &= \text{EEG data, measures} \\
Y &= \text{label (pre-ictal, interictal)} \\
W &= \text{neural network parameters}
\end{align*}
\]

\[
\min_w \{ L(X, Y, W) \} = \min_w \left\{ \sum_i E_w(X_i, Y_i) + \|W\| \right\}
\]

per-sample error

regularization (keep it simple)

loss/risk on training data

Testing dataset “out-of-sample”

\[
\text{new, unseen data}
\]

e.g. same patient, new seizures

\[
N \text{ seizures}
\]

\[
\{1, 2, 3\}
\]

N -fold cross-validation

Training (adjusting parameters \(W\)) = iterative process

\[
\text{stop training}
\]

\[
\text{x-validation}
\]

\[
\text{overfitting}
\]

\[
\text{# iterations}
\]

\[
\text{error}
\]

[Mormann et al, 2006], [LeCun et al, 2006]
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Continuous energy variation
[Linear, univariate, statistical]

Energy ≈ spikes, bursts in EEG activity

Patient B (4 segments of 12h)

Decision threshold
20-min energy + offset

\[ E_{20\text{min}}(t) = \sum_{t' = t \pm 10\text{min}} x(t')^2 + E_{\text{offset}} \]

Moving Average
1-min energy

\[ E_{1\text{min}}(t) = \sum_{t' = t \pm 0.5\text{min}} x(t')^2 \]

Seizure prediction

Prediction horizon 3h
Sensitivity 71%
1 FP every 10h
No statistical validation

[Esteller et al, 2005]
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(Multivariate) linear systems

\[
x(t) = \begin{bmatrix} 0.01x(t-1) + 0.13y(t-1) - 0.1z(t-1) \\
-0.06x(t-1) + 0.52y(t-1) + 0.03z(t-1) \\
-0.5x(t-1) - 0.31y(t-1) - 0.68z(t-1) \end{bmatrix}
\]

Autoregressive linear system of 10th order
Fitting an autoregressive model
[Linear, multivariate, statistical]

Measure of average error made when trying to fit an autoregressive linear model of 4th order to a 10sec window of EEG channels.

Patient B

EEG becomes more like a multivariate linear system during seizures (good for seizure detection)

Sensitivity 0%
Maximum cross-correlation
[Linear, bivariate, statistical]

Cross-correlation between channels
For each channel, choice of delay
giving best cross-correlation

Prediction horizon 3h

Different hypothesis of ↑ or ↓ of
cross-correlation, depending on pairs of channels

All seizures together
Area under ROC = 0.75 (good)

Each seizure separately
Area under ROC = 0.86 (good)

Statistical significance
(surrogates) at 0.05

As good as nonlinear multivariate

[Mormann et al, 2005]
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Our research: classification and regression of bivariate dynamical patterns
Nonlinear dynamical systems
(example: chaotic Lorenz system)

Lorenz = (very) simple model of atmosphere

State $S$ = variables $x$, $y$, $z$ at time $t$

$$\frac{dx}{dt} = -16x + 16y$$

$$\frac{dy}{dt} = 45.92x - y - xz$$

$$\frac{dz}{dt} = -xz - 2z$$

Nonlinear function $f$

$(x, y, z)$ at time $t \rightarrow (x, y, z)$ at time $t + \Delta t$

$S_{t + \Delta t} = f(S_t)$

[Stam, 2005]
Nonlinear dynamical systems
(example: chaotic Lorenz system)

Lorenz = (very) simple model of atmosphere

State $S = \text{variables } x, y, z \text{ at time } t$

\[
\frac{dx}{dt} = -16x + 16y
\]
\[
\frac{dy}{dt} = 45.92x - y - xz
\]
\[
\frac{dz}{dt} = xy - 2z
\]

Nonlinearity

Nonlinear function $f$

$(x,y,z)$ at time $t \rightarrow (x,y,z)$ at time $t+\Delta t$

$S_{t+\Delta t} = f(S_t)$
Nonlinear dynamical systems
(example: chaotic Lorenz system)

Observation (state unknown)

Dynamical reconstruction:
Time-delay embedding

\[ S_t = y(t - \tau), y(t - 2\tau), \ldots, y(t - d\tau) \]

Time delay \( \tau \)
Embedding dimension \( d \)

EEG:
\[ d=7 \]
\[ \tau=5\Delta t \]
Nonlinear dynamical systems
(example: chaotic Lorenz system)

**Observation (state unknown)**

Butterfly effect:
Exponential rate of growth of a small perturbation

\[ |\Delta S_{t+n\Delta t}| = |\Delta S_t|e^{n\lambda} \]

Lyapunov exponent

Local flow =
Average on directions of trajectory

Correlation dimension =
Estimation of dimension of chaotic orbit

EEG: dynamics change with time?
(pre-ictal, ictal, post-ictal, interictal...)

[Stam, 2005]
Dynamical Entrainment
[Nonlinear, bivariate, statistical]

Short-term Lyapunov exponent (computed over 10sec) decreases (i.e., stability of EEG trajectory increases) before seizure entrainment.

Prediction horizon >1h
Sensitivity 82%
1 FP every 8h
No statistical validation

T-index = average difference of STL between electrodes in optimal onset zone

[Iasemidis et al, 2005]
Nonlinear interdependence

Time-delay embedding
Of \( x(t), x(t-\tau), \ldots, x(t-d\tau) \) is \( x(t) \)

EEG channel \( i \) and time series \( x_i \)
Time indices of \( K \) nearest neighbors of \( x_i(t) \)
\[ \{ t_1^i, t_2^i, \ldots, t_K^i \} \]

EEG channel \( j \) and time series \( x_j \)
Time indices of \( K \) nearest neighbors of \( x_j(t) \)
\[ \{ t_1^j, t_2^j, \ldots, t_K^j \} \]

\[
R(t, x_i) = \frac{1}{K} \sum_{k=1}^{K} \left\| x_i(t) - x_i(t_k^i) \right\|_2^2
\]

\[
R(t, x_i | y_j) = \frac{1}{K} \sum_{k=1}^{K} \left\| x_i(t) - x_i(t_k^j) \right\|_2^2
\]

\[ S(x_i | x_j) = \frac{1}{N} \sum_{t=1}^{N} \frac{R(t, x_i)}{R(t, x_i | x_j)} \]

Similarity between the trajectories of channels \( i \) and \( j \) using the reconstruction error

Phase locking, synchrony

Phase locking = phase synchrony (Wavelet or Hilbert transforms)

[Le Van Quyen et al, 2005], [Mormann et al, 2005]
Phase-locking value (synchrony) [nonlinear, bivariate, algorithmic]

**Phase Locking Value**
= average phase difference

**Feature vectors of PLV**: 15 frequencies \times (20 \times 19 / 2) electrodes

**Reference library** of 5 to 10 clusters of PLV feature vectors (interictal synchrony)

**Outliers** = preictal PLV vectors

**K-means**

**Student t-test** for selection of discriminant PLV features

**Chi-square test** for detection of outliers

[Le Van Quyen et al, 2005]
Phase-locking value (synchrony) [nonlinear, bivariate, algorithmic]

**preictal alarm:**

Outliers rate > threshold (in short time window)

Prediction horizon > 3h
Sensitivity 69%
Many FP
No statistical validation

[Le Van Quyen et al, 2005]
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Classification of dynamical bivariate features (1)

EEG data
- Public EEG database at Albert-Ludwigs-Universität in Freiburg
  - 21 patients
- NYUMed EEG database (supplied by Vanessa Arnedo, Ruben Kuzniecky)
  - So far 4 patients

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>112 iEEG (56 in bipolar)</th>
<th>5 days</th>
<th>4 seizures</th>
<th>Left frontal epilepsy focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 2</td>
<td>126 iEEG (63 in bipolar)</td>
<td>12 days</td>
<td>7 seizures</td>
<td>Lateral frontal epilepsy focus</td>
</tr>
</tbody>
</table>

Step 1: Generate from EEG, every 5sec, bivariate features

- Maximal cross-correlation
- Dynamical entrainment
- Phase-locking synchrony
- Nonlinear interdependence
Classification of dynamical bivariate features (2)

Step 2:

- **Phase-locking synchrony**
- Group bivariate features into short "movies" (1 min or 5 min)

Examples of ictal synchrony movies
Classification of dynamical bivariate features (2)

Step 2: Group bivariate features into short “movies” (1min or 5min)

Examples of pre-ictal synchrony movies
Classification of dynamical bivariate features (2)

Step 2: Group bivariate features into short “movies” (1min or 5min)

Phase-locking synchrony

Examples of interictal synchrony movies
Example from Freiburg using:
- 1min patterns
  (12 frames of 5sec)
- Cross-correlation
- 6 channels
  (3 onset zone, 3 outside)
i.e. $6 \times 5/2 = 15$ pairs

Freiburg data:
4 types of patterns

Non-frequentual features:
- Cross-correlation
- Nonlinear interdependence
- Difference of Lyapunov exponents
- 1min: $12 \times 15 = 180$ features
- 5min: $60 \times 15 = 900$ features

Frequency-specific features (7 freq bands):
- Phase locking synchrony
- Entropy of phase difference
- Wavelet coherence
- 1min: $12 \times 15 \times 7 = 1260$ features
- 5min: $60 \times 15 \times 7 = 6300$ features

(a) EEG on 06-Dec-2001, 12:00 (interictal)
(b) Features C on 06-Dec-2001, 12:00 (interictal)
(c) EEG on 12-Dec-2001, 06:20 (preictal)
(d) Features C on 12-Dec-2001, 06:20 (preictal)
Classification of dynamical bivariate features (3)

Step 3: 

Train and test nonlinear classifiers using Machine Learning

Unsupervised clustering
1. Uncover unique clusters
2. Optimize choice of features, movie length...

Supervised classification

Interictal
Pre-ictal

[Mirowski, Madhavan, LeCun, Kuzniecky, 2006]
Machine learning classification

- Neural networks:
  - Logistic regression
  - L1 regularization
  - Feature selection by looking at weights
- Convolutional networks
  - L1 regularization
  - Feature selection by input sensitivity analysis
- SVM
## Results on Freiburg dataset

<table>
<thead>
<tr>
<th></th>
<th>pat 1</th>
<th>pat 2</th>
<th>pat 3</th>
<th>pat 4</th>
<th>pat 5</th>
<th>pat 6</th>
<th>pat 7</th>
<th>pat 8</th>
<th>pat 9</th>
<th>pat 10</th>
<th>pat 11</th>
</tr>
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<tbody>
<tr>
<td>C</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0.79</td>
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<tr>
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<td>0.40</td>
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<table>
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*Note: The table shows the results for different models and datasets.*
An innovative approach

1. **Integrate dynamical data**
   i.e. evolution of synchronization

2. **Nonlinear classification**
   learnt from data (*machine learning*)
   (instead of simple threshold-based decision)

3. **Feature selection**
   which **channels** at which **frequencies** are discriminative of seizures?

4. **Remaining problem:**
   - Time to seizure: what is the preictal duration?
   - (Instead of interictal vs. preictal **classification**)

- Epilepsy Foundation grant proposal
  (August 2008)


Jouny C., Franaszczuk P., Bergey G., Signal complexity and synchrony of epileptic seizures: is there an identifiable preictal period, *Clinical Neurophysiology* 2005

Lehnertz K., Litt B., The first international collaborative workshop on seizure prediction: summary and data description, *Clinical Neurophysiology* 2005


