Chaos, Brain and Epilepsy: A Feedback Systems approach

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and

- American Epilepsy Research Foundation
- Ali Paris Fund for LKS research and education
- Cyberonics

Outline

- Our problem: some intriguing observations
- Dynamical entrainment as a seizure predictor (drug, electrical stimulation)
- Electrical stimulation results
- Seizure control concepts
- Simulation models
- Focus localization

Our Problem

- Looking for a mechanism of seizure generation and ways to control them
- Simulation models to study fundamental issues
  - coupling, entrainment (synchronization), seizures
- Design of feedback controllers for seizure suppression
  - controllability, observability
  - control objectives
- Implementation Issues

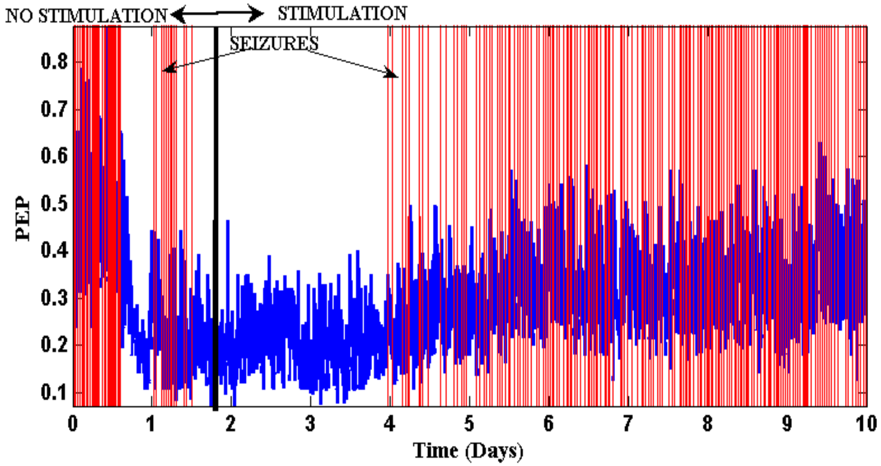
Electrical Stimulation as a Treatment for Epilepsy

- No systemic and central nervous system side effects
- Periodic (fixed-form) stimulation: biphasic pulses
  - Cyberonics (Vagus nerve, US FDA approved), Medtronic, Neuropace (deep brain stimulation)
  - Recent results: still not a complete solution
  - 30% of patients experience >50% reduction of seizure frequency but < 10% become seizure free
- Frequency of waveform conjectured to correlate to excitatory-inhibitory actions

Proposed approach

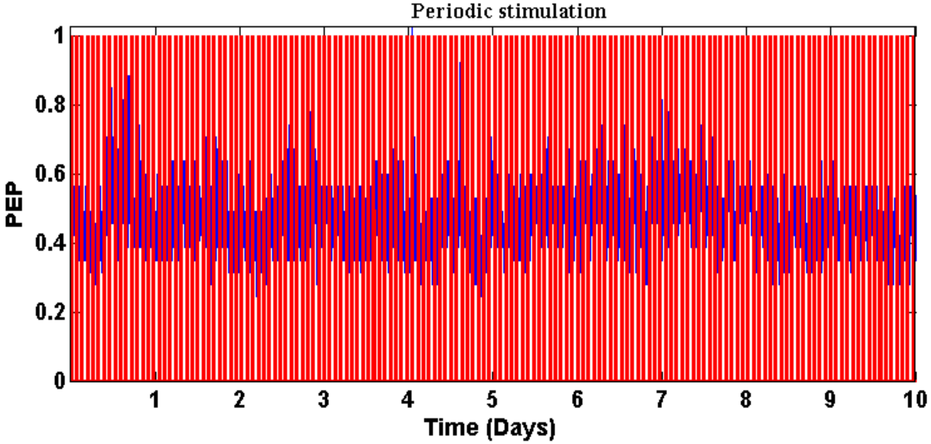
- Feedback decoupling
  - Taking advantage of postulated structure
- Multivariable sensing and control
  - Multiple electrode signal processing to reveal focus, entrainment sites, and disrupt pathologies
  - Identifying system changes in coupling and stability
- Discrete decisions modulating a suitable waveform
  - Control impulses are defined at the us level but stimulation evolves at seconds or minutes time-scales

Epileptic Brain Stimulation Results

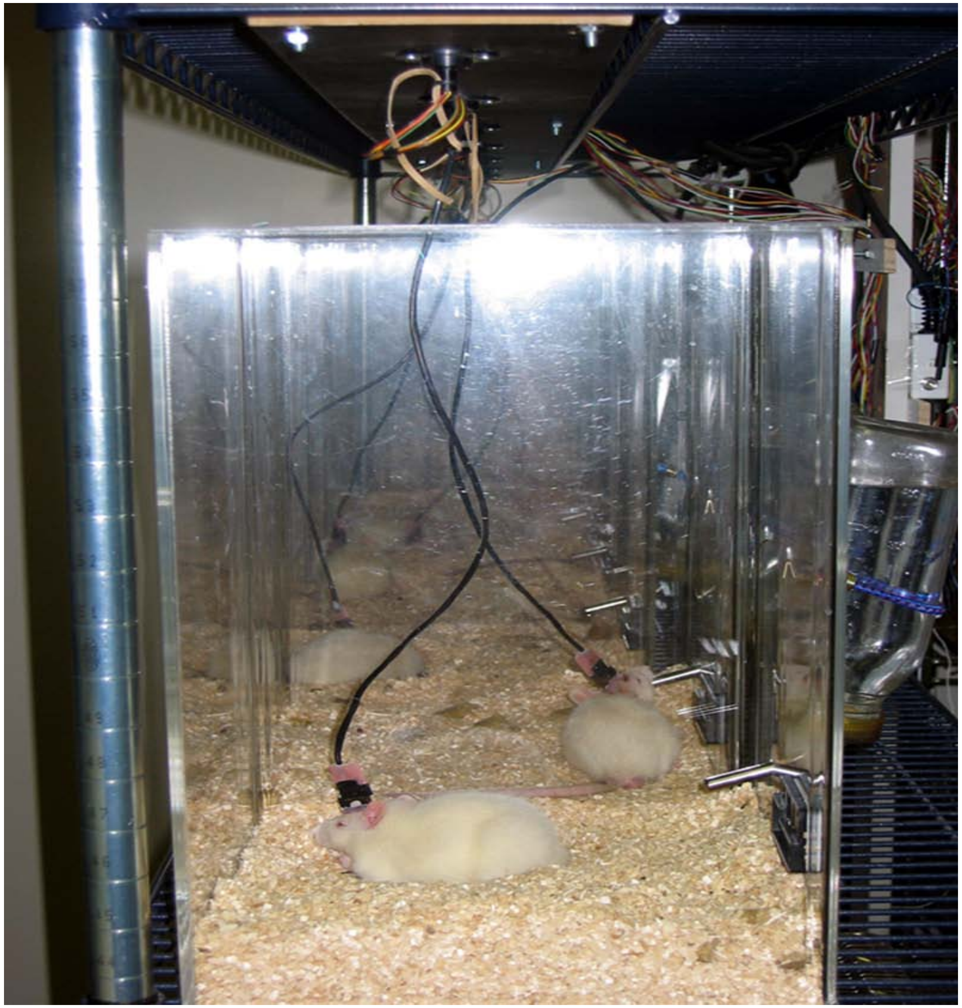


Warning–based stimulation of epileptic brain (thalamus) in rat leads to reduction of seizure frequency. But after the 4th day, the entrainment measure (PEP) increases and seizures reappear despite continuing stimulation, indicating loss of effective seizure control.

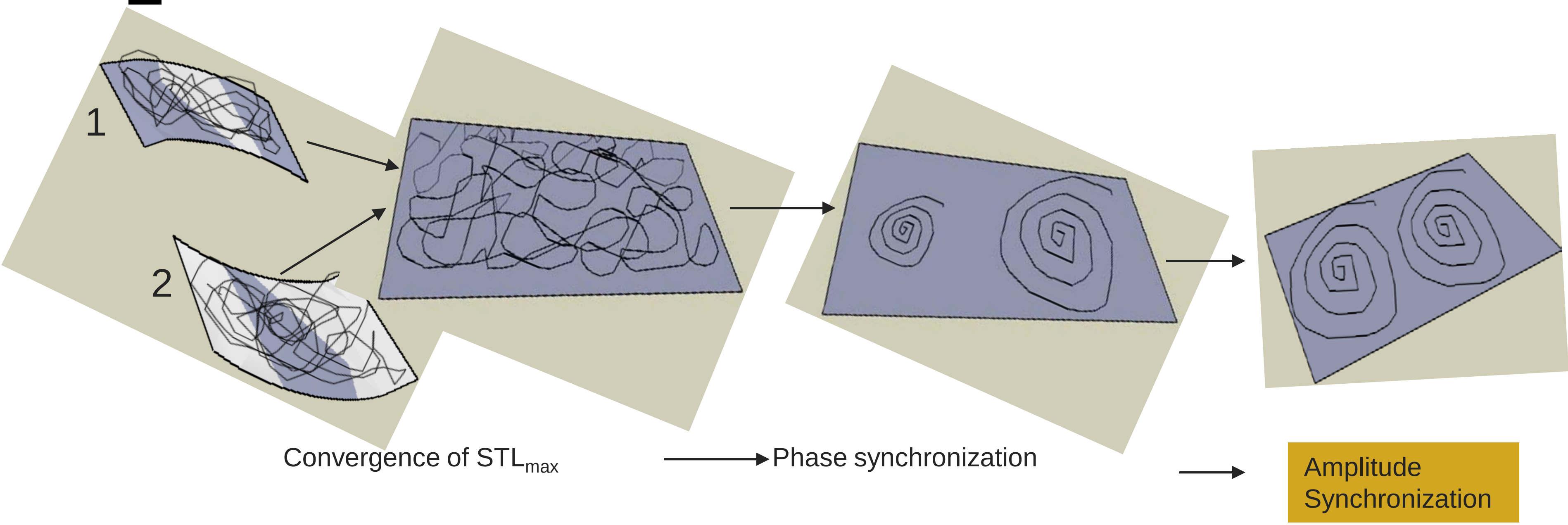
In the same rat, perodic stimulation shows no reduction in the entrainment measure (PEP) of brain sites, nor in seizure frequency.



Rat EMU: Low-light CCTV video camera multiplexed system, Grass-Telefactor Beehive® Millennium EEG monitoring stations, Plexiglas cages and commutator wiring



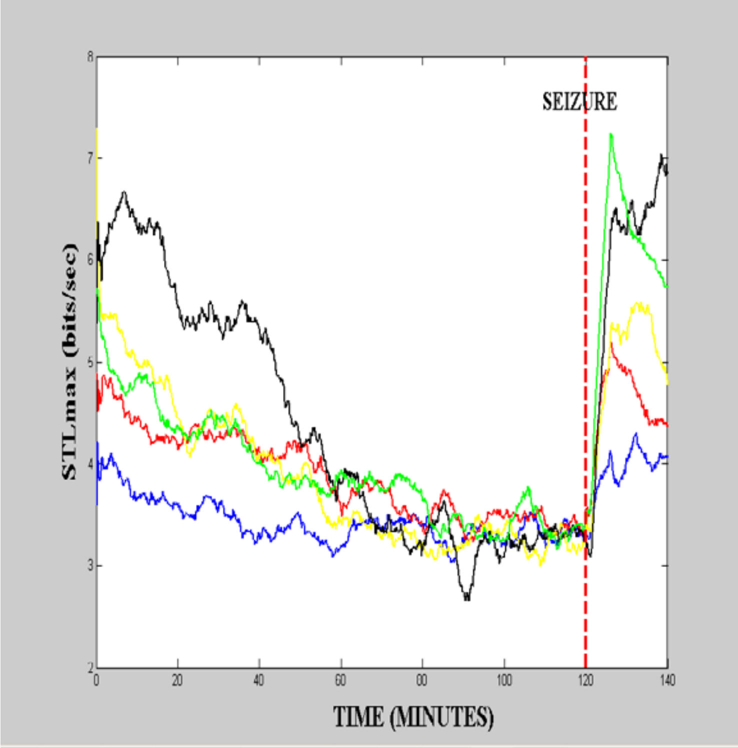
BASIC PRINCIPLES I: Dynamical Entrainment at two brain sites

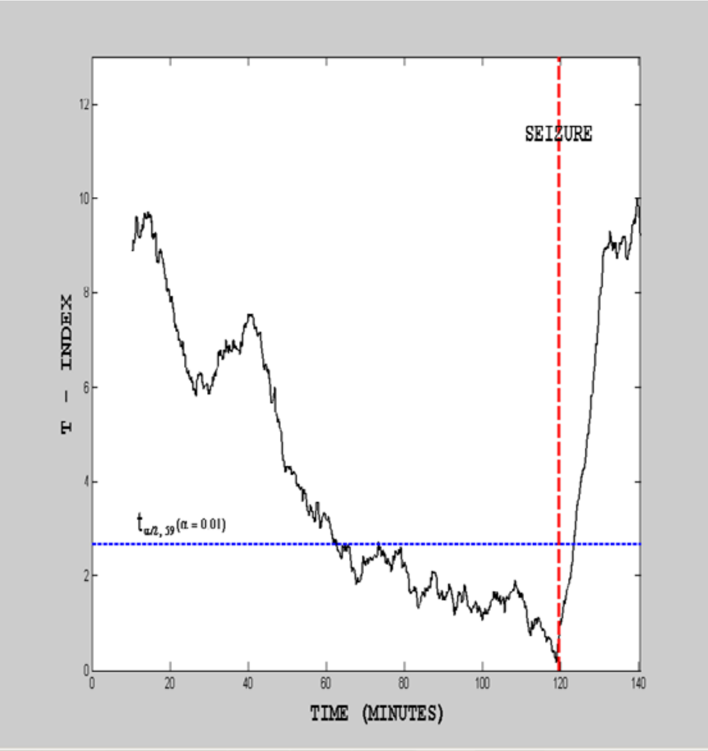


I. <u>The Principle of Dynamical Entrainment</u>
II. <u>The Principle of Dynamical Disentrainment</u>
III. <u>The Principle of Resetting</u>

Dynamical entrainment: Convergence of Chaos at multiple brain sites over time

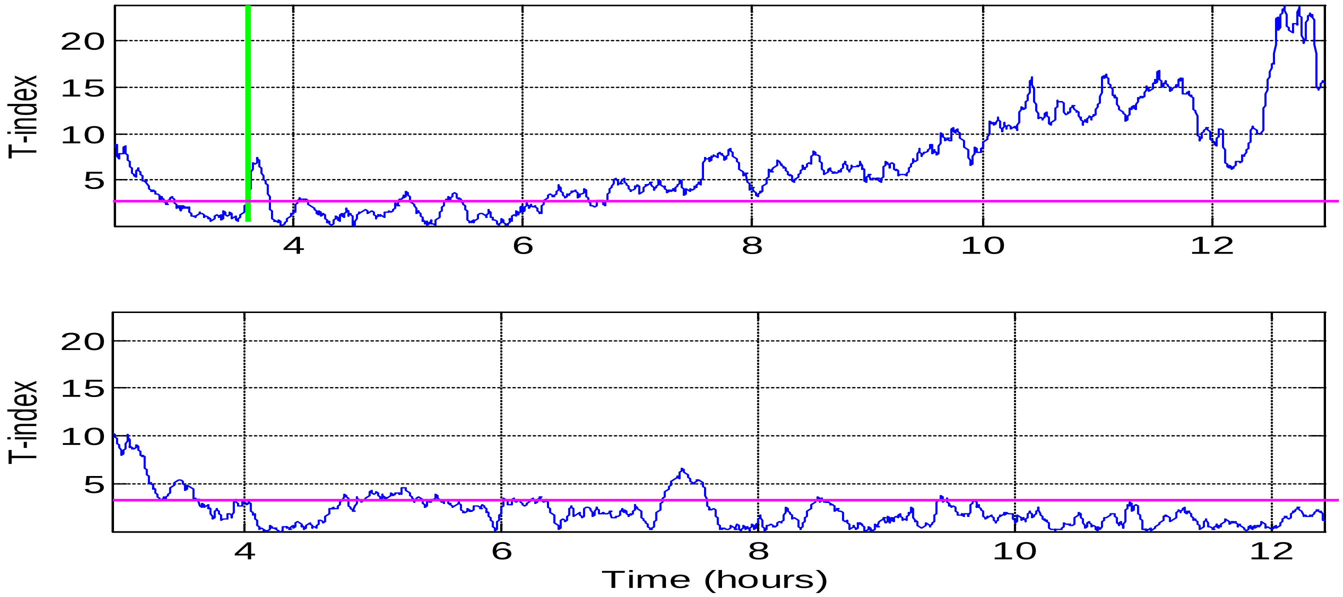
Maximum Short-term Lyapunov Exponent (STLmax) and T-index profiles over time; entrainment and resetting



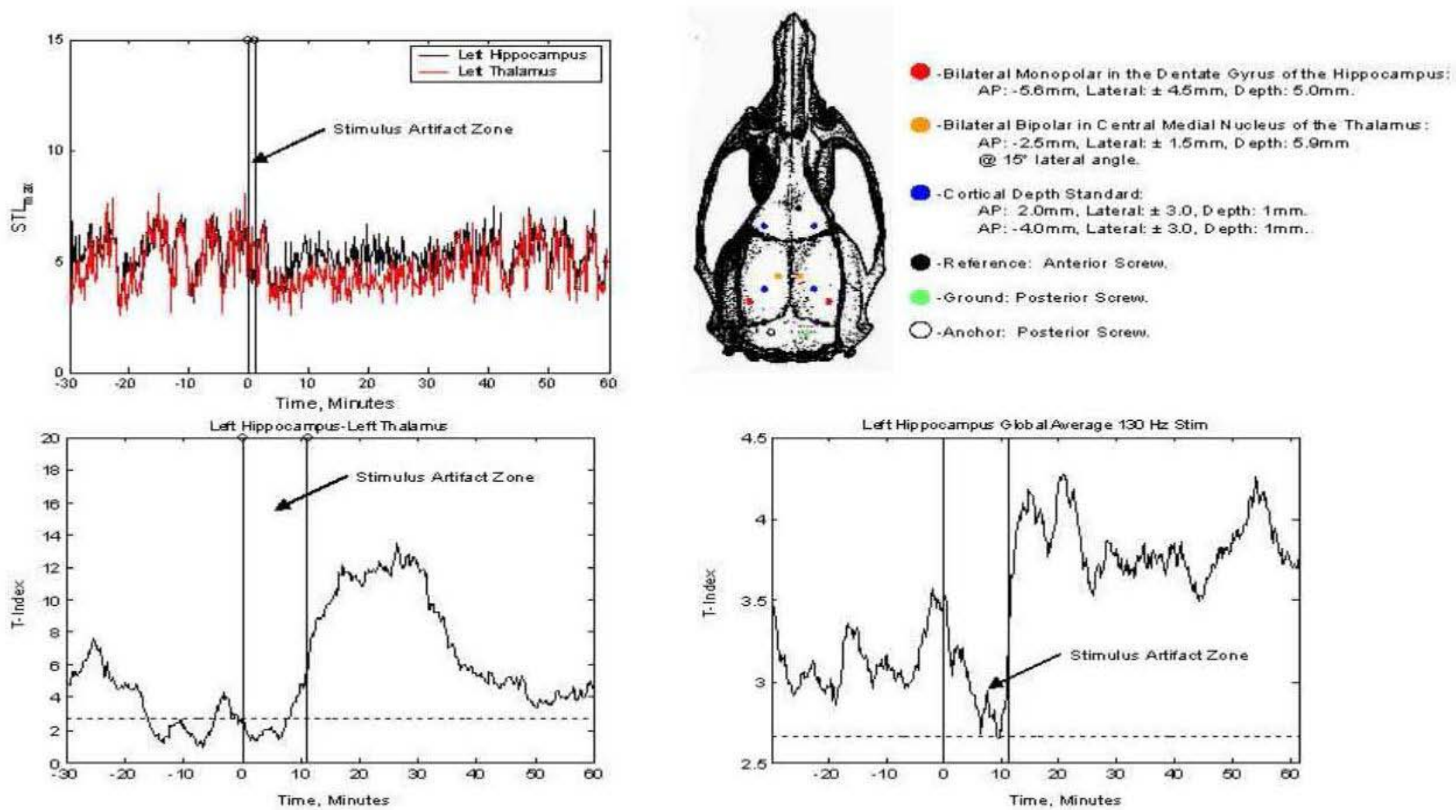


AEDs and Brain Resetting: Animal model

Lithium-pilocarpine induced SE rodent model: AED treatment results to long-term resetting of brain dynamics. No AED treatment results to no resetting

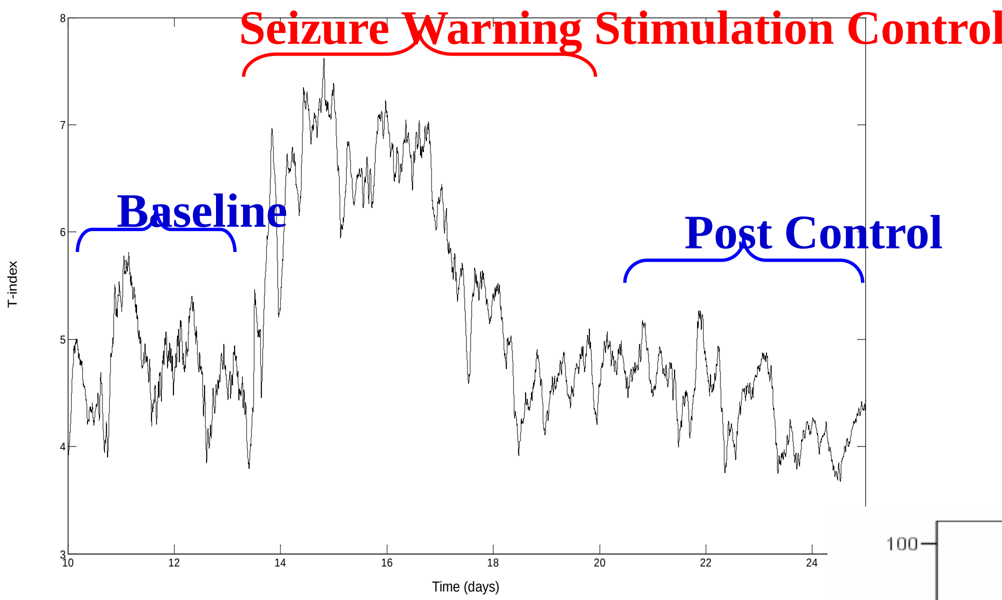


ANIMAL STUDIES: ELECTRICAL STIMULATION



- 130Hz electrical stimulation (constant current square biphasic pulses of 100 msec width, intensity of 750 mA and duration of 1 minute applied to the left thalamic electrode)

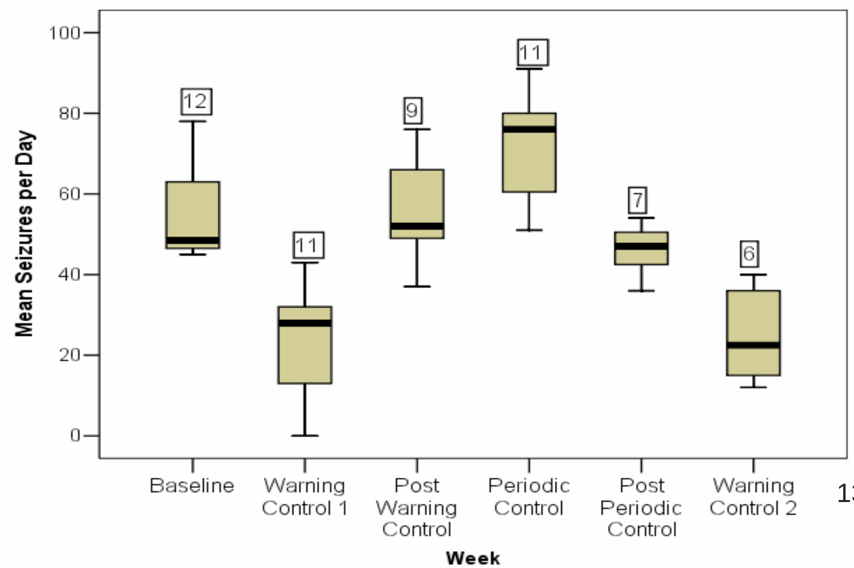
Epileptic Brain Stimulation Results



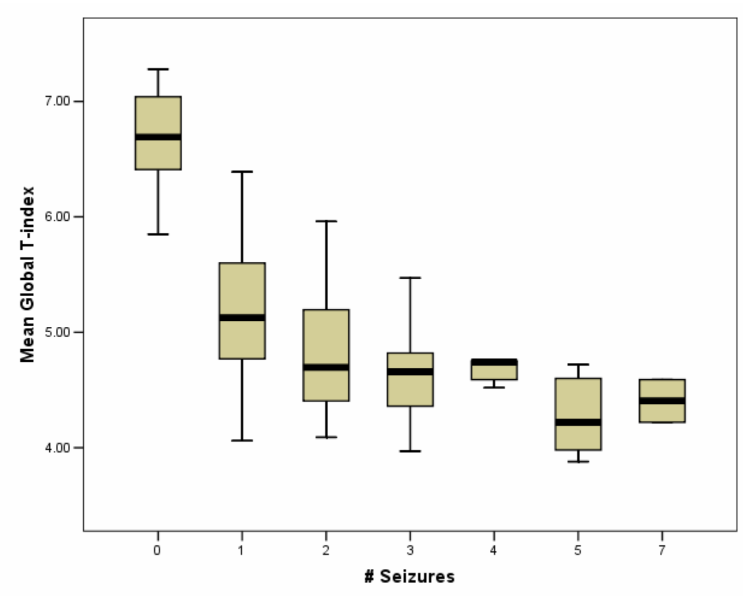
SYNCHRONIZATION DETAILS BEFORE, DURING AND AFTER CONTROL.

"T-index synchronization measure:" When elevated, there are no seizures. When control is lost, T-index level drops back to baseline levels and seizures return.

STATISTICALLY QUANTIFIED REDUCTION OF SEIZURES WITH CONTINUOUS FEEDBACK

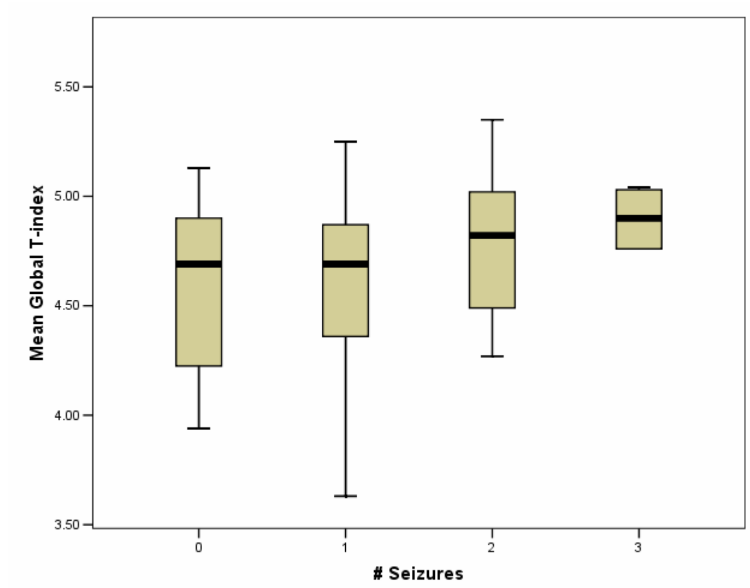


Epileptic Brain Stimulation Results



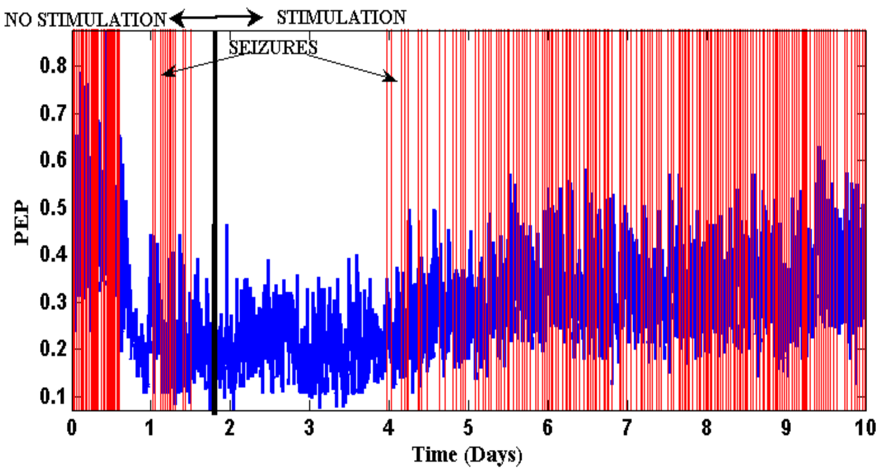
CORRELATION BETWEEN T-INDEX LEVEL AND SEIZURE FREQUENCY IN RESPONDING RATS.

LACK OF CORRELATION BETWEEN T-INDEX LEVEL AND SEIZURE FREQUENCY IN NON-RESPONDING RATS.



L.B. Good, S. Sabesan, S.T. Marsh, K. Tsakalis, L.D. Iasemidis & D.M. Treiman, "Automatic seizure prediction and deep brain stimulation control in epileptic rats," American Epil.Soc., 2007.

Epileptic Brain Stimulation Results



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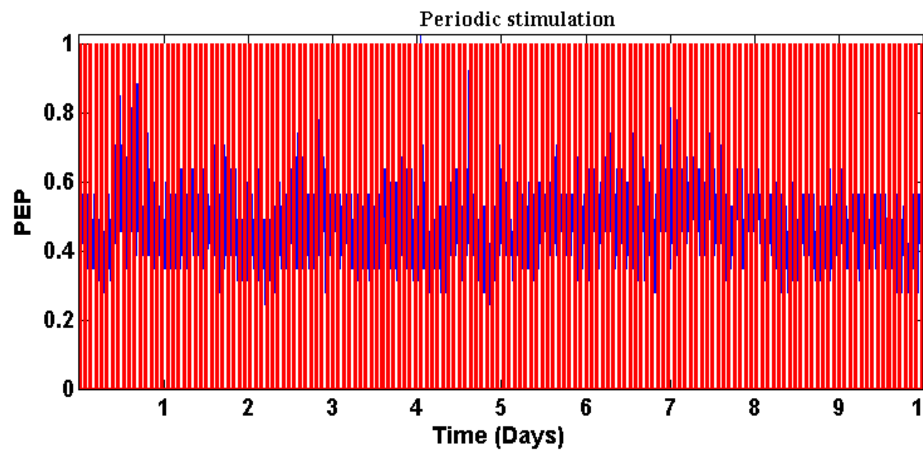
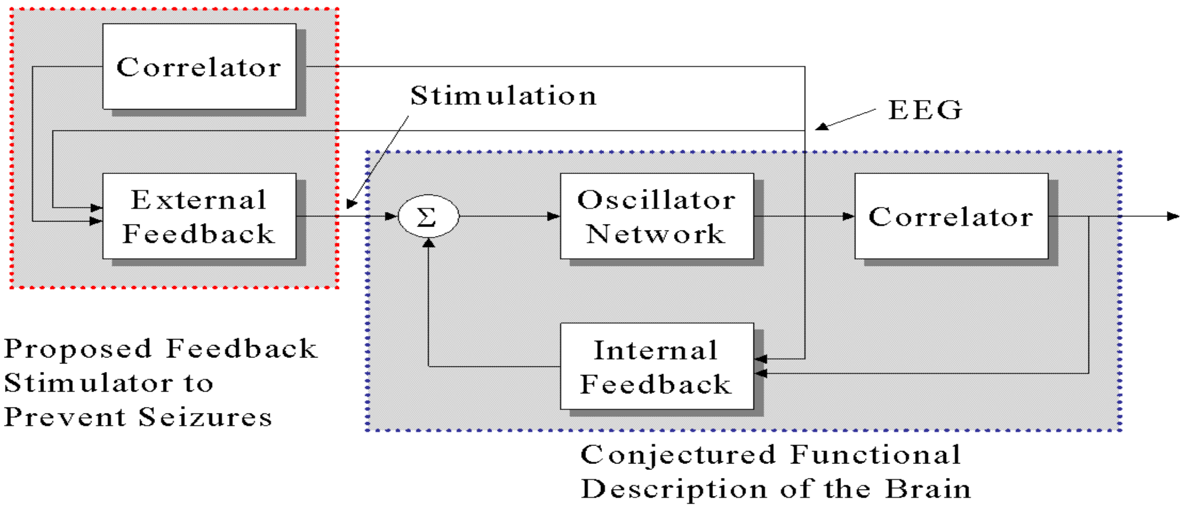


Midpoint conclusions

- Entrainment metrics correlate well with seizure occurrences
- With respect to the same metrics, electrical stimulation can suppress seizures as an alternative to drugs
- Stimulation points should not be “random,” both in location and timing
  - Should break-up abnormal entrainment, instead of initiating one
  - Early detection and localization of entraining sites are important

BASIC PRINCIPLES II: Feedback Control Model



1. Normal brain: Internal feedback disentrains the entrained brain sites fast
2. Epileptic Brain: Pathology in the internal feedback fails to disentrain the epileptogenic focus from the normal brain sites fast enough

Key Observations

- Spatially distributed properties vs. lumped ones
  - coupling and synchronization
  - network vs. cell/group destabilization
- Seizure controllability correlates well with the ability to disentrain the brain
  - Seizure frequency was reduced when the stimulation achieved disentrainment
  - Seizure frequency was not reduced when the stimulation did not affect entrainment

Conjectures

1. Seizures are predictable on the basis of dynamical entrainment
2. Seizures reset the brain dynamics
3. Electrical stimulation and/or AEDs can reset the brain. Then seizures do not occur.
4. “Where,” “How,” “When” to stimulate

Simulation models of epileptic seizures: interconnected chaotic oscillators

- Various simulation models (Traub, Freeman, daSilva, Iassemidis)
- General functional characteristics but not necessarily precise prediction
  - mechanisms of seizure generation
  - Epilepsy as a system characteristic
- Importance of interconnections (coupling)
  - Seizures as a network property
- Feedback for homeostasis
  - with learning interpretations
- Suggestions for viable feedback control strategies

Simulation models of epileptic seizures: interconnected chaotic oscillators

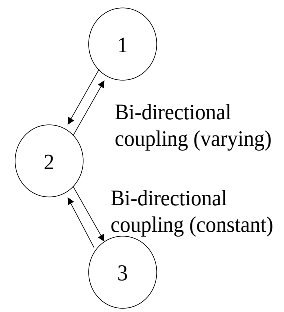
- Coupled oscillator models show synchronization but no instability

$$\frac{dx_i(t)}{dt} = -\omega_i y_i - z_i + \sum_{j=1, i\neq j}^{N} (\varepsilon_{i,j} x_j - \varepsilon'_{i,j} x_i) + \sum_{j=1, i\neq j}^{N} u^{I}{}_{i,j}$$

$$\frac{dy_i(t)}{dt} = \omega_i x_i + \alpha_i y_i$$

$$\frac{dz_i(t)}{dt} = \beta_i x_i + z_i (x_i - \gamma_i)$$

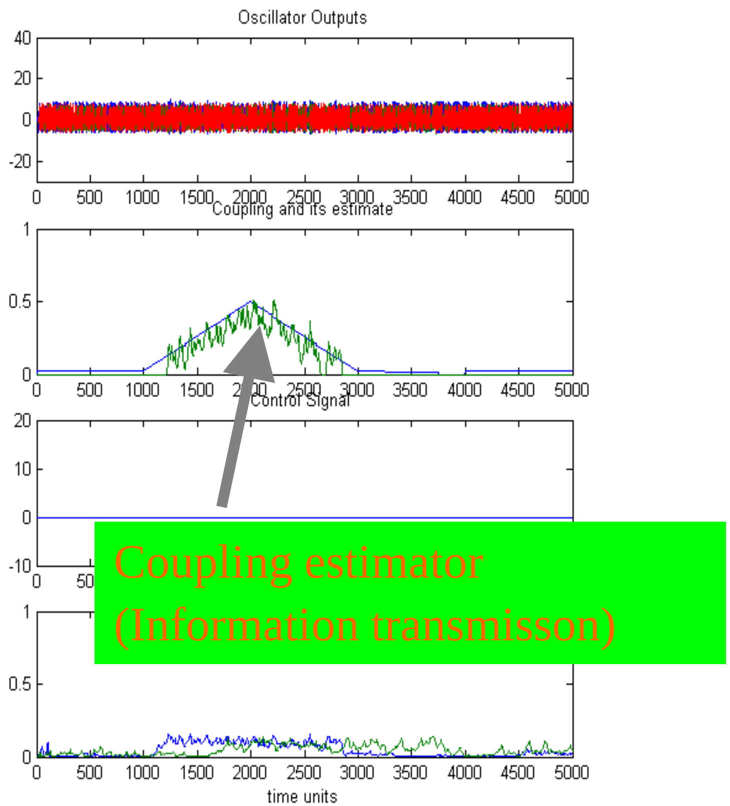
$$u_{ij}^{I} = k_{ij}^{I} (x_i - x_j), \quad k_{ij}^{I} = PI^{I}\{corr[x_i, x_j] - c^*\}$$

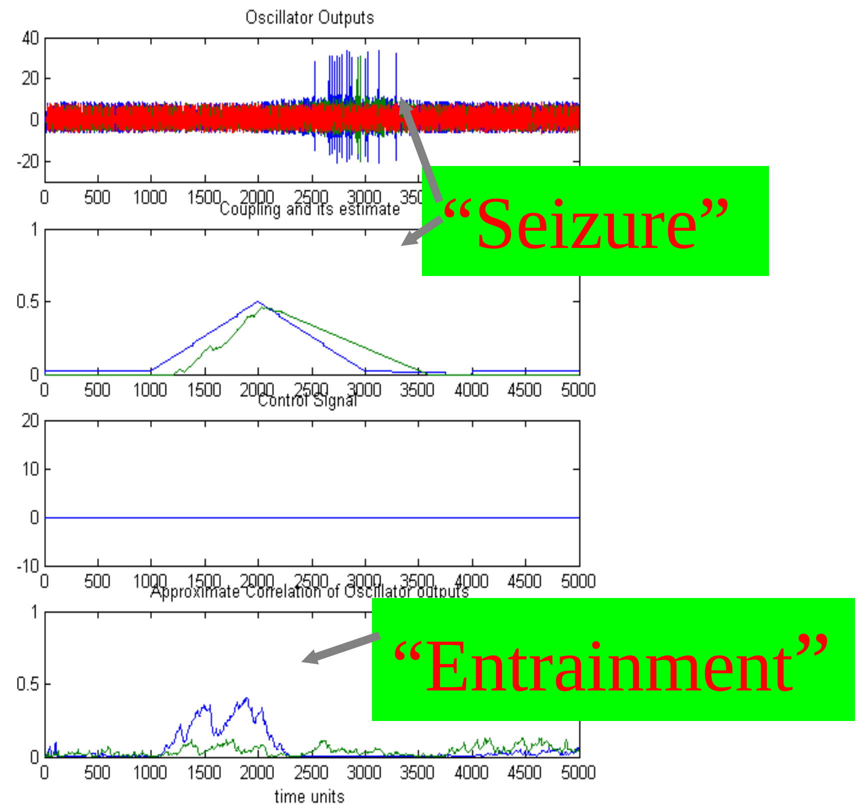


Oscillator interconnections for the MATLAB "brain emulator"

- Internal feedback - local destabilization
  - Parameter adaptation-like term: feedback gain k_{ij}

Model seizure details



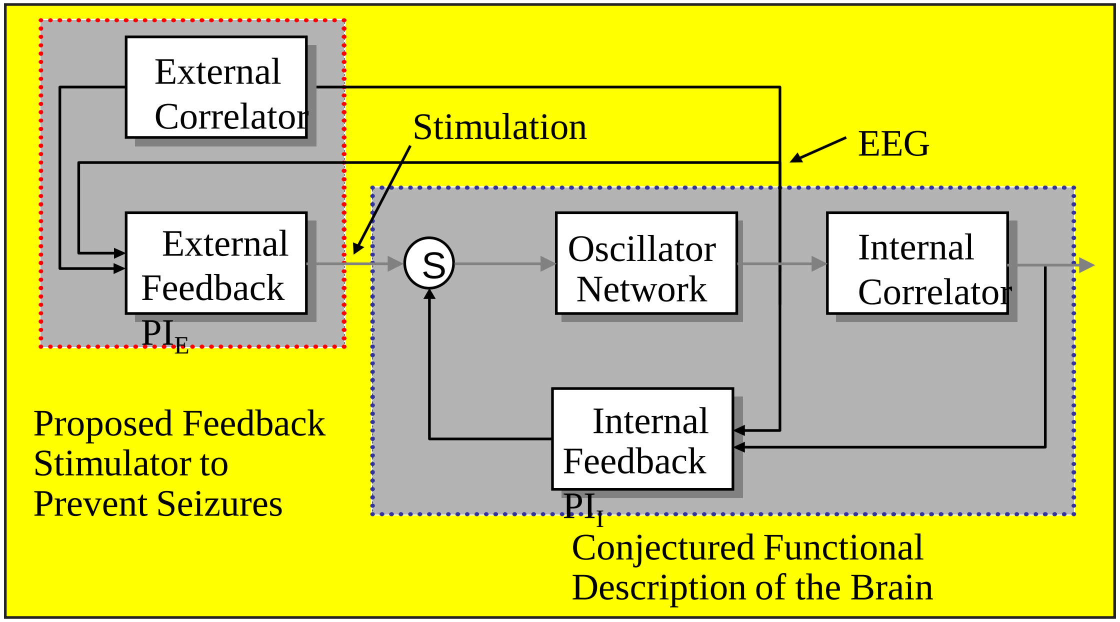


"Normal" "Epileptic"

Tsakalis, CDC 2005

Details on controller design

- Definition of the Control Objective:
  - Stabilization?
  - Model Matching?
  - Desynchronization?



- Recover normal operation by undoing the pathology: Feedback Decoupling
  - – Minimal interference

Details on controller design

$$\frac{dx_i(t)}{dt} = -\omega_i y_i - z_i + \sum_{j=1, i\neq j}^{N} (\varepsilon_{i,j} x_j - \varepsilon'_{i,j} x_i) + \sum_{j=1, i\neq j}^{N} u^I{}_{i,j} \boxed{+ \sum_{j=1, i\neq j}^{N} u^E{}_{i,j}}$$

$$\frac{dy_i(t)}{dt} = \omega_i x_i + \alpha_i y_i \qquad \frac{dz_i(t)}{dt} = \beta_i x_i + z_i (x_i - \gamma_i)$$

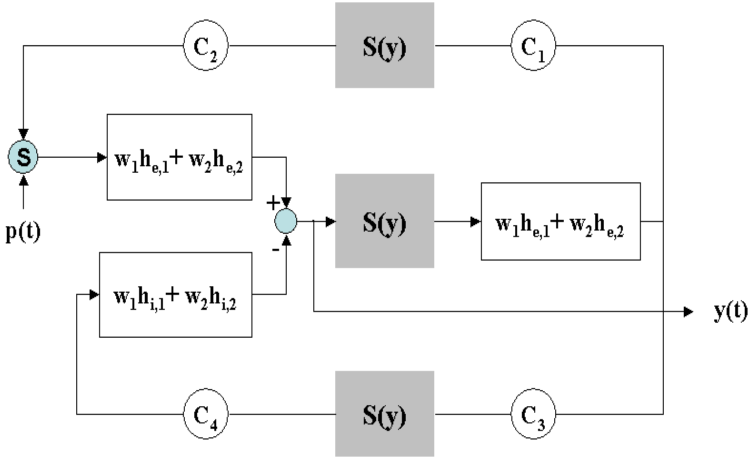
$$u_{ij}^I = k_{ij}^I (x_i - x_j), \quad k_{ij}^I = PI^I \{corr[x_i, x_j] - c^*\}$$

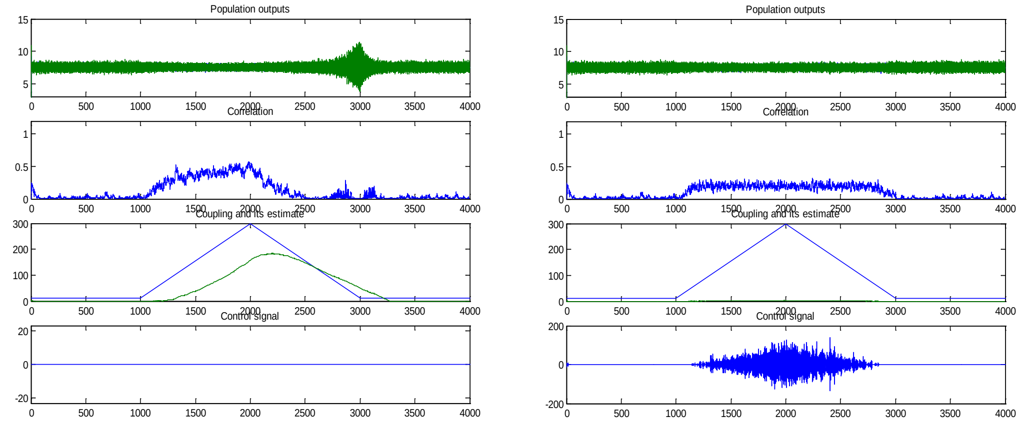
$$\boxed{u_{ij}^E = k_{ij}^E (x_i - x_j), \quad k_{ij}^E = PI^E \{corr[x_i, x_j] - c^*\}}$$

- Adaptive feedback decoupling
- Design of a PI controller/estimator
- Recovery of normal behavior

Neurophysiology-based models

- The occurrence of seizures and their control via feedback decoupling have been verified in various neuron population models that have been proposed in the literature.
  - Jansen’s model of cortical neural mass, modified by David and Friston



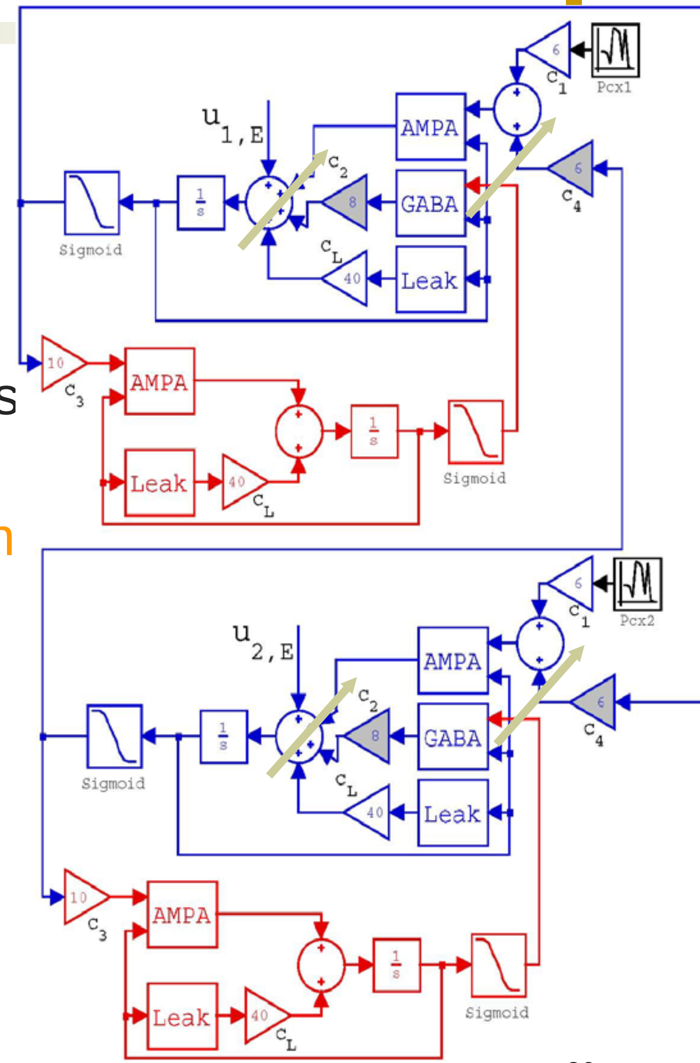


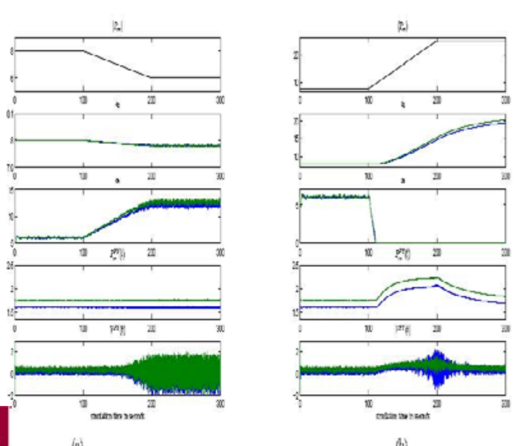
» Jansen, Zouridakis, Brandt, ``A neurophysiologically-based mathematical model of flash visual evoked potentials”, Biological Cybernetics, 68, 275-283, 1993

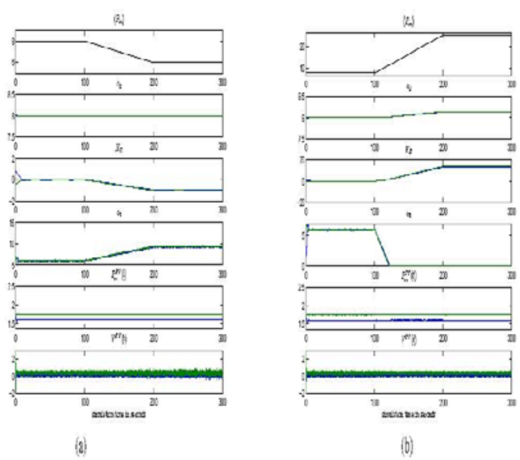
» David and Friston, ``A neural mass model for MEG/EEG: coupling and neuronal dynamics”, NeuroImage, 20, 1743-1755, 2003

Neurophysiology-based models

- Interacting cortical populations
  (Suffczynski et al. 2004)
- homeostasis: balance of inhibition-excitation
- interconnection through excitatory neurons only (AMPA)
- c2, c4: PI feedback adjustment to maintain an average firing rate output
- lack of adjustment can cause seizure-like bursts







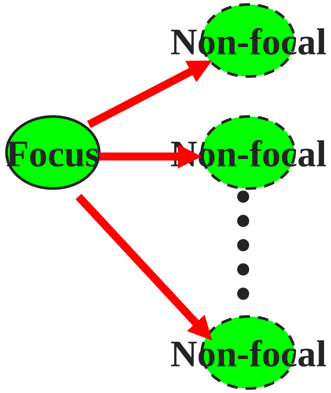
Midpoint conclusions

- Simulation models suggest a general strategy for stimulation
  - Biphasic train of pulses disentraining two sites
  - Duration of stimulus interpreted as PWM of the control signal
- Narrowing down the stimulation sites
  - T-index still used as the main entrainment signal
  - Focus Localization techniques to remove some pairs based on long-term trends

A dynamical view of focus localization

- **Dynamical view of Focus Localization**:

  Epileptogenic focus acts as the driver for all electrodes → preictally, highly synchronized network.



Existing Approaches

- Synchronization-based measures
  - "Pure" measures: Cross-correlation, Cross-coherence, **Mutual Information**
  - "Hybrid" measures: T-index based dynamical measures
- Directional measures
  - Parametric measures: Multi-variate local –linear AR/ARMA, global error reduction models
  - Non-parametric measures: **Transfer Entropy**

Quantifying causal interactions

- Transfer Entropy (TE): Measure of information flow

$$TE(Y \to X) = \sum_{n=1}^{N} P(x_{n+1}, x_n^{(k)}, y_n^{(l)}) \log \frac{P(x_{n+1} \mid x_n^{(k)}, y_n^{(l)})}{P(x_{n+1} \mid x_n^{(k)})}$$

***$P(x_{n+1}|x_n^{(k)})$*:** a priori transition probability of process X

***$P(x_{n+1}|x_n^{(k)}, y_n^{(l)})$*:** the true underlying transition probability of the combined process of X and Y.

Problems

k, l: How to select them ?

r: How to select the optimal radius for multi-dimensional probability estimation

Improvements

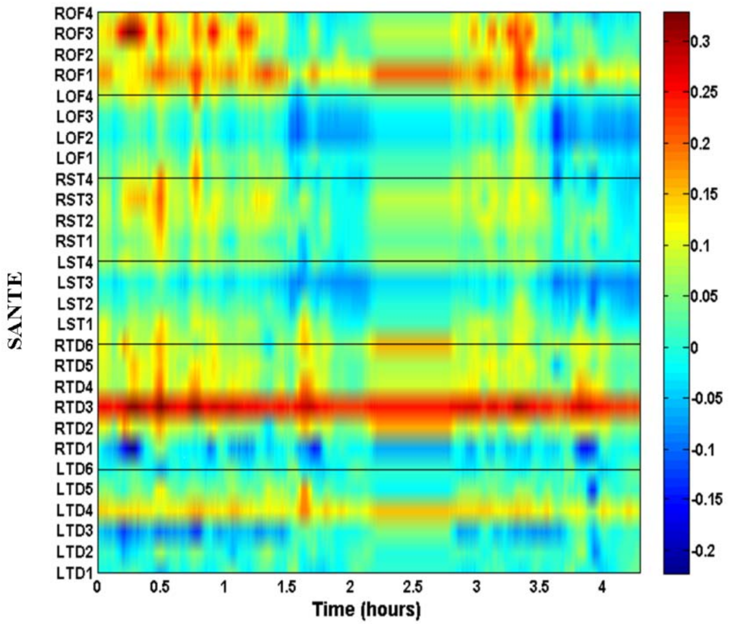
k: first minimum of mutual information

l =1; l>1 for indirect connections

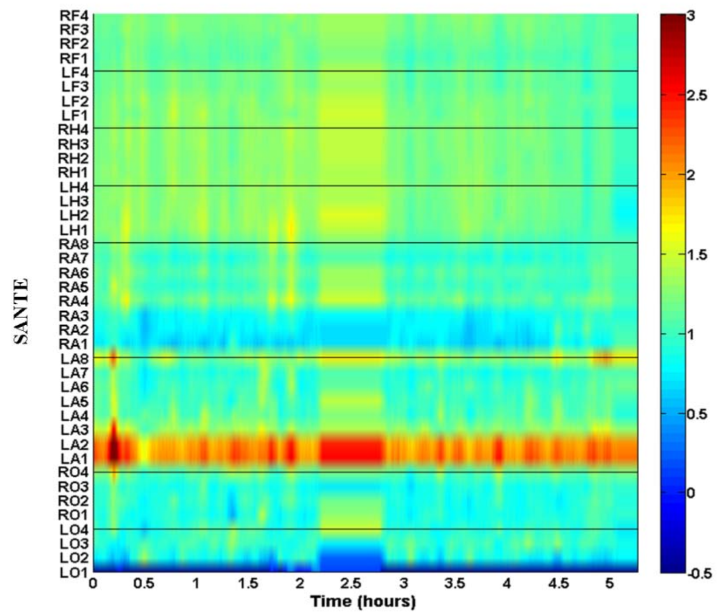
r: TE was averaged at an intermediate range of r (σ/5-2σ/5)

SANTE over time, short term (depth EEG data, 4 patients)

Focus: RTD2, RTD3



Focus: LA1, LA2, LA3



Hypothesis: The epileptogenic focus drives other brain sites for the longest period of time

SANTE over time, long-term: Focus localization results

Probability of driving

$$P_D(i) = \frac{1}{NT}\sum_{t=1}^{NT}\Theta(SANTE^t(i) > 0)$$

Outlier detection method using Chebyshev inequality

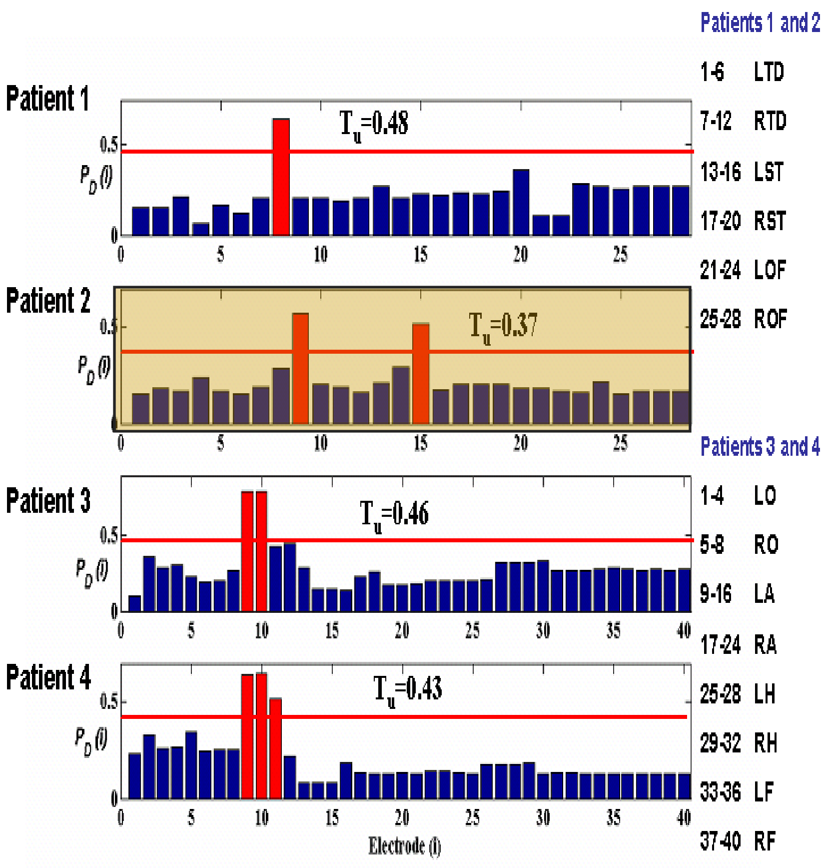
$$P(|X-\mu| \geq k\sigma) \leq \frac{1}{k^2}$$

Two Stage Process:

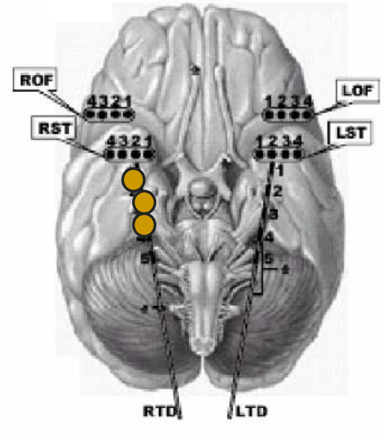
Stage 1: Choose p=0.1→Calculate *k*--> remove outliers→ Estimate sample μ and σ

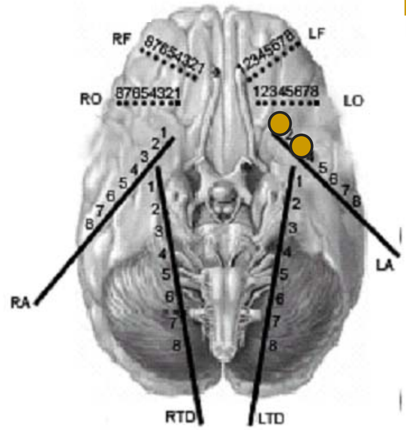
Stage 2: Choose p=0.01→Calculate *k*--> Estimate Threshold

$$T_u = \mu + k\sigma$$



Focus localization results: Summary





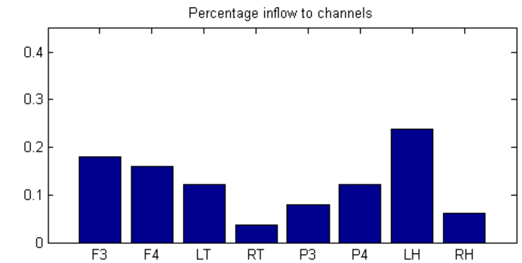
PATIENT ID	Focus (clinical assessment)	Focus localization (*SANTE* and P_D)	Focus lateralization (*SANTE* and P_D)
Patient 1	Right temporal lobe (RTD: RTD2, RTD3)	Right temporal lobe (RTD2)	Right hemisphere Right temporal lobe (RTD)
Patient 2	Right temporal lobe (RTD: RTD3, RTD4)	Right/Left temporal lobe (RTD3>LST3)	Right+Left hemisphere Right/Left temporal lobe (RTD, LST)
Patient 3	Left Amygdala (LA: LA1, LA2, LA3)	Left Amygdala (LA1> LA2)	Left hemisphere Left Amygdala (LA)
Patient 4	Left Amygdala (LA:LA1, LA2, LA3)	Left Amygdala (LA1> LA2> LA3)	Left hemisphere Left Amygdala (LA)

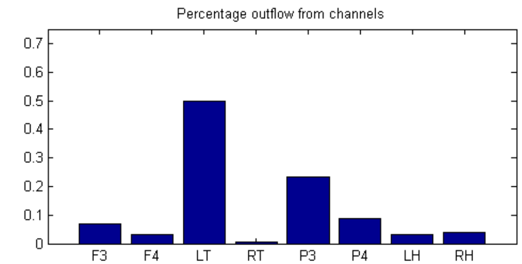
Focus localization for real-time applications

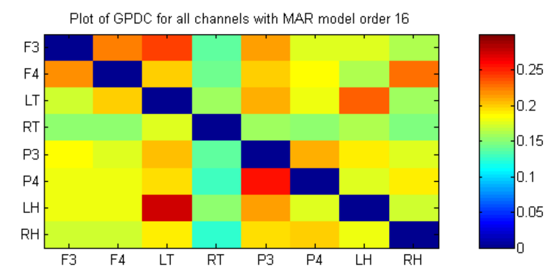
- Estimation of directional information flow between different brain sites yields a fast (real-time) method for focus localization that has comparable performance to our best results so far.
  - Generalized Partial Directed Coherence [Baccala 2007], Grubb's outliers test for detecting electrode sites with frequent across time and high across sites connectivity level
- Focus localization from intracranial recordings of 9 **epileptic patients** with known, clinically assessed foci.
  - In 6/9 patients focus localization was successful with high statistical significance, $\alpha=0.01$. In the other 3 only at $\alpha=0.1$
- The epileptic focus appears to have the highest connectivity

Focus localization for real-time applications

- GPDC application to the animal model shows the LT as the main (effective) focal site with LT-LH as the most active pair.
- This is consistent with previous observations that the Lithium-Pilocarpine model causes increased activity and damage on the Thalamus.
  - RT here was a damaged electrode
  - Data fitting for the directed coherence calculations is reasonably good for 10-30sec data
- Emerging multivariable control model of stimulus effect to desynchronization







Discussion

Seizure Predictability

characteristic changes prior to a seizure's electrographic onset across seizures in the same patient and across patients.

Seizure Prediction

real-time prospective algorithm that can reliably detect the preictal changes early

Seizure Resetting

inability of the epileptic brain to reset begets seizures.

AEDs, electrical stimulation reset the brain too.

Seizure Susceptibility – Ictogenesis:

A dynamical view: brain's homeostatic mechanisms for resetting of dynamical entrainment do not function properly

Seizure Control

biologically plausible computer simulation models, electrical stimulation animal models, and Status Epilepticus drug studies

Epileptogenic Focus Localization

important byproduct of the dynamical analysis

Discussion

- Models of interacting populations (neuropysiology-based) used to guide the prediction and control
  - coupling-induced seizures, synchronization
- Conjectured model structure suggests a potentially viable control strategy
  - neurophysiological effect of electrical stimulation, charge balance, tissue damage, etc. to be addressed
  - Unified treatment algorithms for AED and electrical stimulation
- Single-electrode stimulation may be the limiting factor for reliable reduction of seizure frequency
  - Simple strategies may be inadequate to suppress all seizures
- Tackling the multivariable problem in prediction (changes in coupling) and control (stimulating pairs of electrodes)

Selected Journal Publications

1. L.B.Good, S. Sabesan, S.T. Marsh, K. Tsakalis, D.M. Treiman, L.D. Iasemidis, ``Nonlinear Dynamics of Seizure Prediction in a Rodent Model of Epilepsy,'' Nonlinear Dynamics, Psychology and Life Sciences, v.14, 5, 411-434, 2010.
2. S. Sabesan, L.B. Good, K.S. Tsakalis, A. Spanias, D.M. Treiman, L.D. Iasemidis, ``Information Flow and Application to Epileptogenic Focus Localization From Intracranial EEG,'' IEEE Transactions on Neural Systems and Rehabilitation Engineering, Volume 17, Issue 3, 244 - 253, June 2009.
3. L.B. Good, S. Sabesan, S.T. Marsh, K. Tsakalis, D.M. Treiman, L.D. Iasemidis, ``Control of Synchronization of Brain Dynamics Leads to Control of Epileptic Seizures in Rodents,'' International Journal of Neural Systems (IJNS), V.19, Issue: 3, pp. 173-196, 2009.
4. N. Chakravarthy, K. Tsakalis, S. Sabesan, L. Iasemidis, "Homeostasis of Brain Dynamics in Epilepsy: A Feedback Control Systems Perspective of Seizures," Annals of Biomedical Engineering Volume 37, 3, 565-585, 2009.
5. N. Chakravarthy, S. Sabesan, L.D. Iasemidis, K. Tsakalis, "Modeling and controlling synchronization in a neuron-level population model", *Int. J. Neural Systems,* vol. 17, pp. 123-138, 2007.
6. K. Tsakalis & L.D. Iasemidis, "Control aspects of a theoretical model for epileptic seizures", *Int. Journal of Bifurcations and Chaos*, vol. 16, pp. 2013-2027, 2006.
7. Chaovalitwongse, L.D. Iasemidis, P.M. Pardalos, P.R. Carney, D.-S. Shiau, and J.C. Sackellares, "Performance of a Seizure Warning Algorithm Based on Nonlinear Dynamics of the Intracranial EEG", *Epilepsy Research*, vol. 64, pp. 93-113, 2005.
8. L.D. Iasemidis, D-S Shiau, P.M. Pardalos, W.Chaovalitwongse, K. Narayanan, A. Prasad, K. Tsakalis, P. Carney & J.C. Sackellares, "Long-term prospective on-line real-time seizure prediction", *J. Clin. Neurophysiol.,* vol. 116, pp. 532-544, 2005.