Feedback Control for Epileptic Seizure Suppression

K. Tsakalis , Electrical Engineering
Arizona State University
tsakalis@asu.edu

Credits

Collaboration

Prof. Leon Iasemidis (Harrington Dept. of Bioengineering)
Prof. David Treiman M.D. (Barrow Neurological Inst. Phoenix, AZ)

Dr. Niranjan Chakravarthy
Dr. Levi Good
Dr. Shivkumar Sabesan

Support

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Ali Paris Fund for LKS research and education

Outline

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

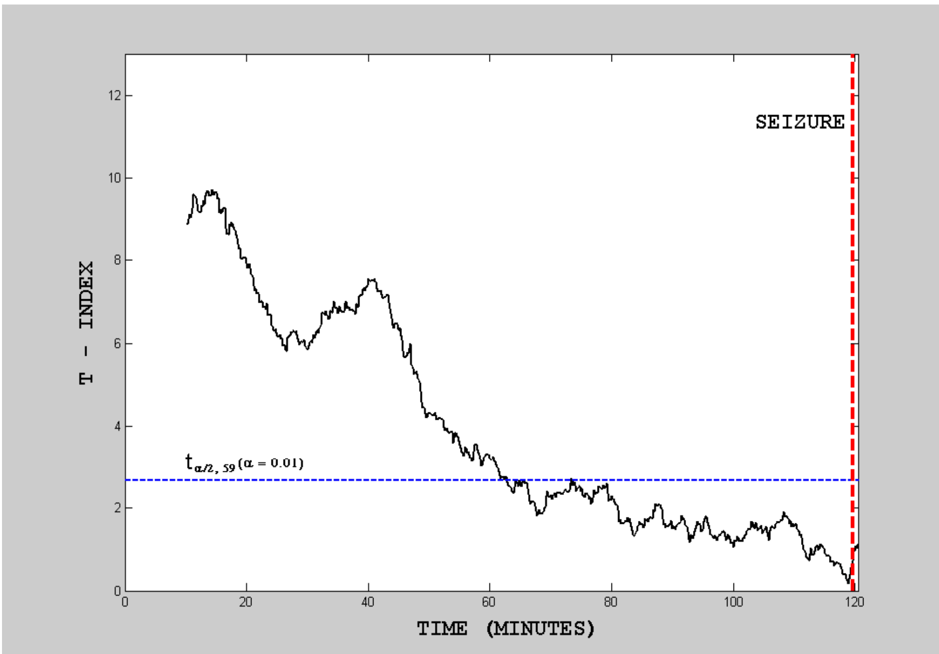
Our Problem

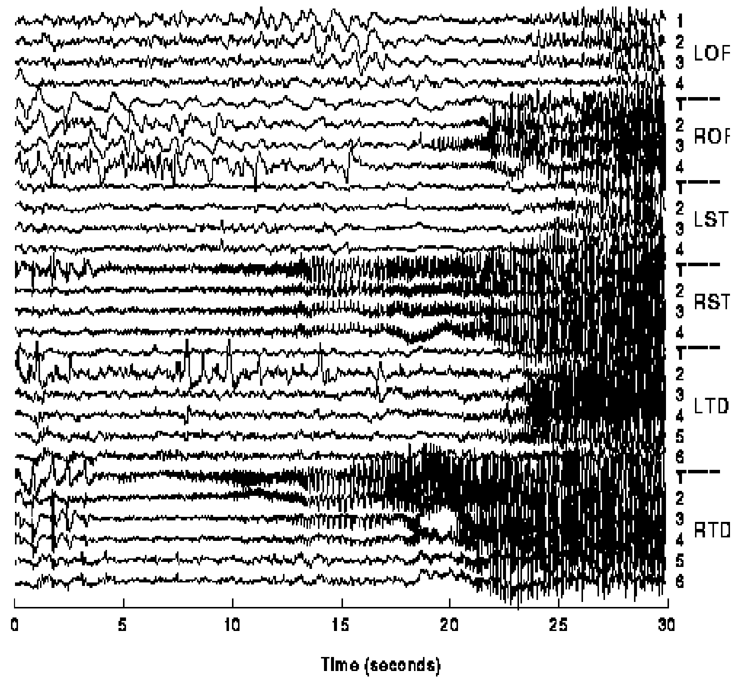
- Looking for a mechanism of seizure generation and ways to control them
- Simulation models to study fundamental issues
  - coupling, entrainment (synchronization), seizures
- Design of feedback controllers for seizure suppression
  - controllability, observability
  - control objectives

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
- Proposed: feedback decoupling (taking advantage of postulated structure)

Average T-index over multiple sites



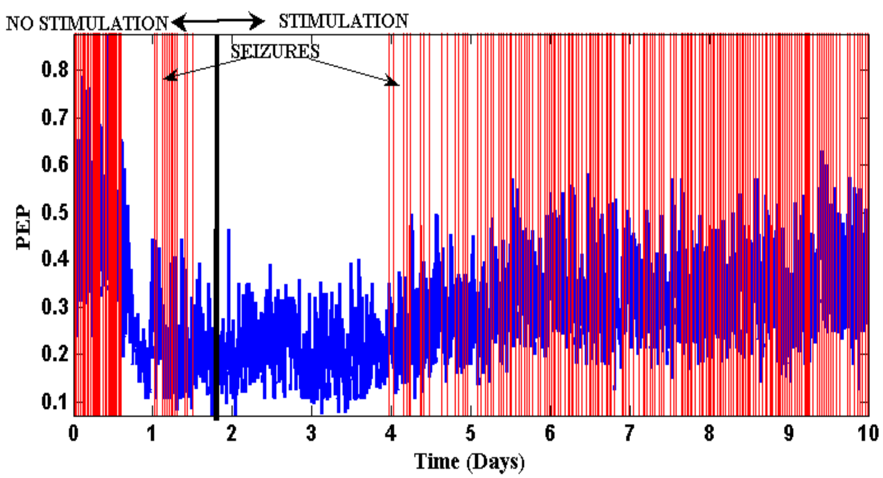


Synchronization/entrainment of brain sites indicates upcoming seizures (or, at least, susceptibility to them)

Iasemidis, 1997

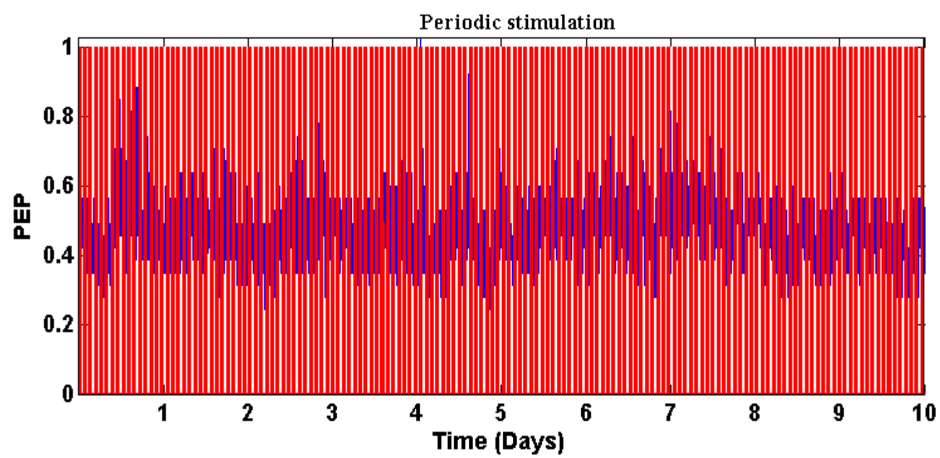
Some Observations

Epileptic Brain Stimulation Results: feedback v. feedforward

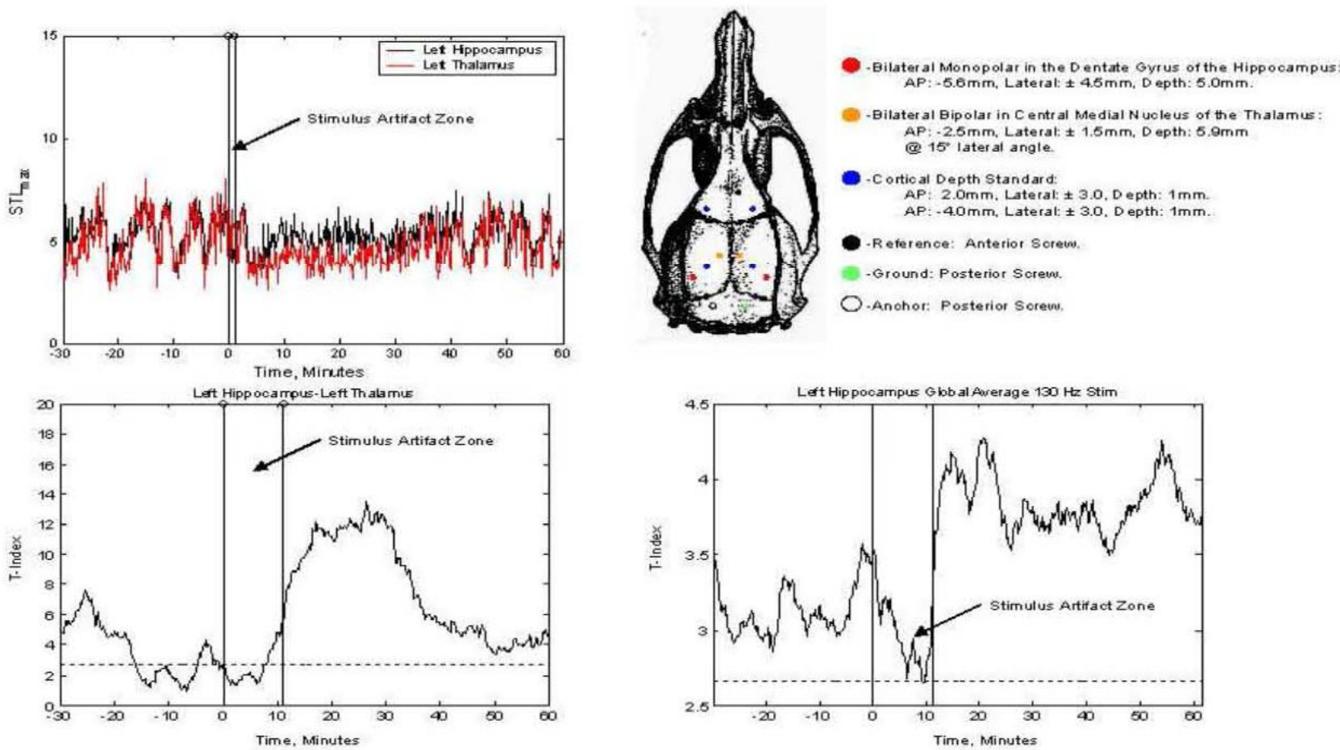


Warning–based stimulation of epileptic brain (thalamus) in rat leads to reduction of seizure frequency. But after the 4th day, the entrainment measure (PEP) increases and seizures reappear despite continuing stimulation, indicating loss of effective seizure control.

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



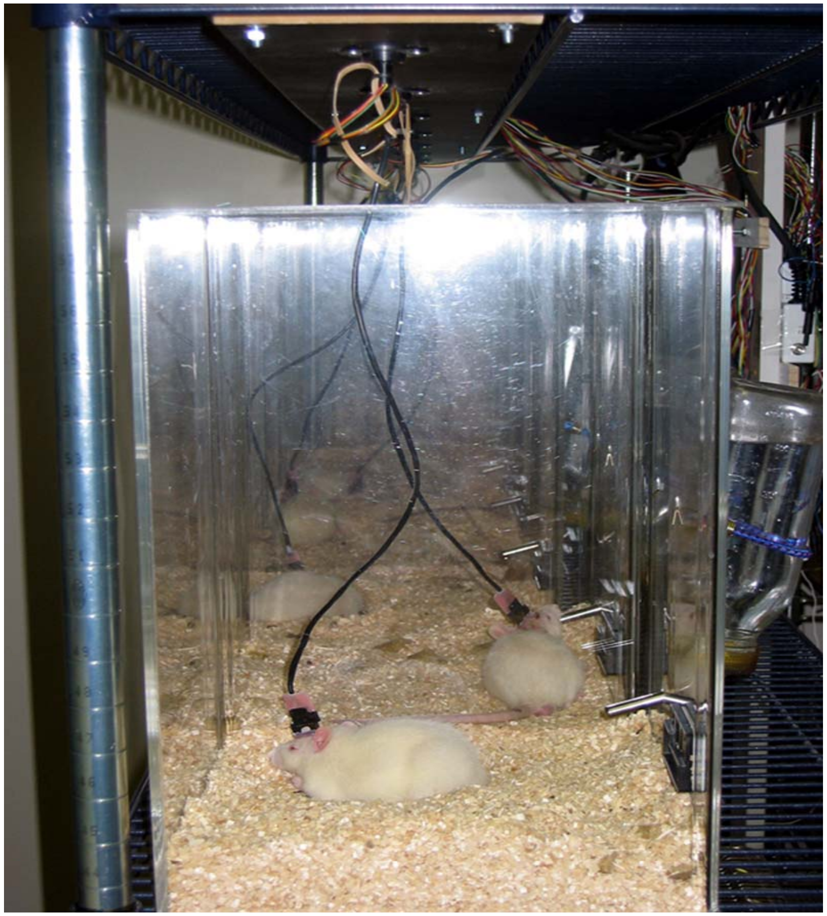
ANIMAL STUDIES: ELECTRICAL STIMULATION



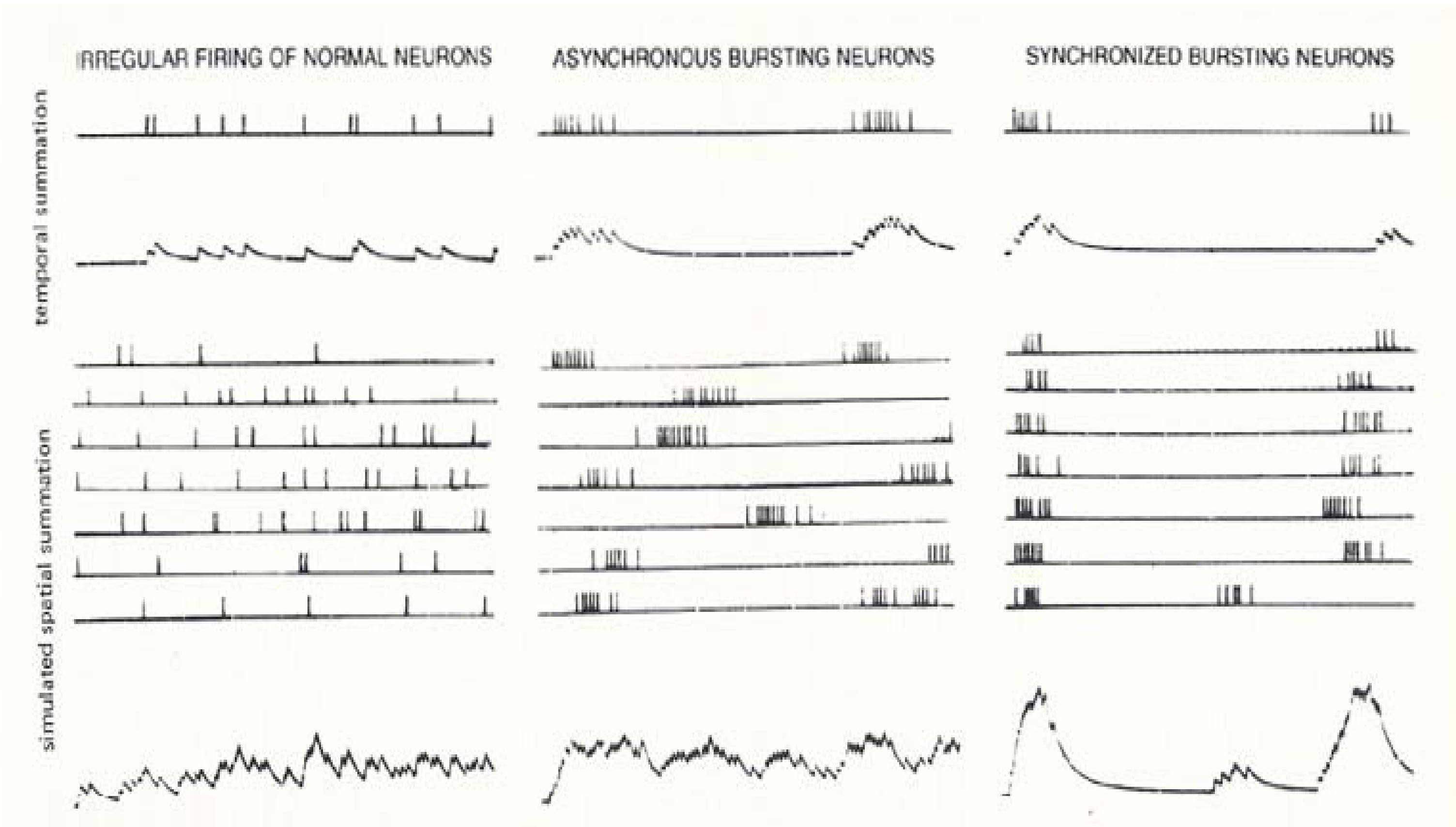
- 130Hz electrical stimulation (constant current square biphasic pulses of 100 msec width, intensity of 750 mA and duration of 1 minute applied to the left thalamic electrode)

Some Observations

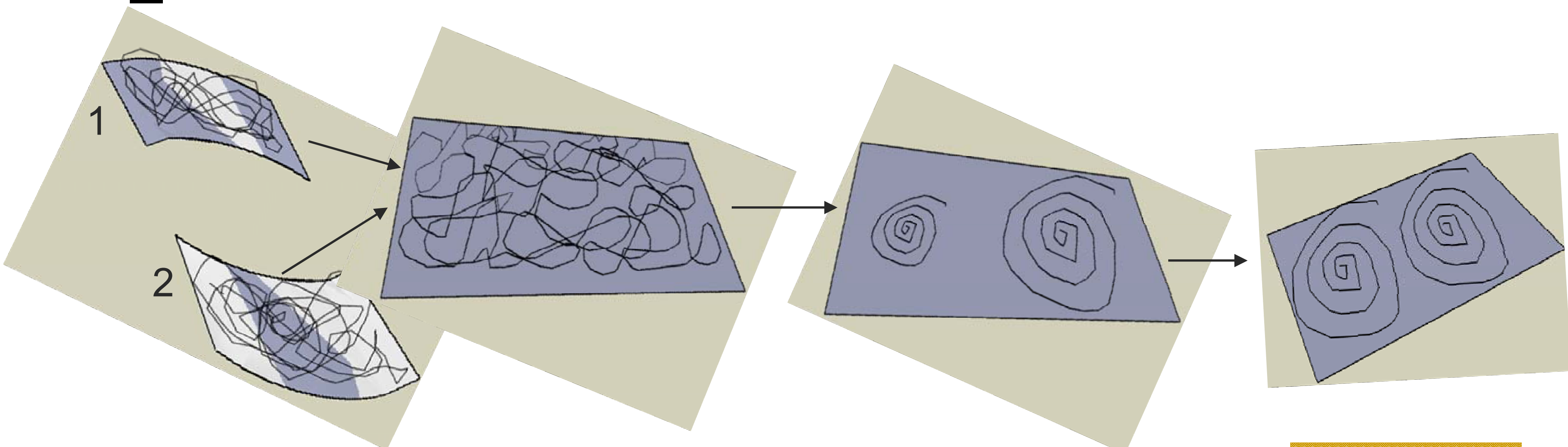
Rat EMU: Low-light CCTV video camera multiplexed system, Grass-Telefactor Beehive® Millennium EEG monitoring stations, Plexiglas cages and commutator wiring



From Microscopic to Macroscopic Level: Temporal and Spatio-Temporal summation



Epilepsy: Dynamical Entrainment, Disentrainment and Resetting



Convergence of STL_{max} → Phase synchronization → Amplitude Synchronization

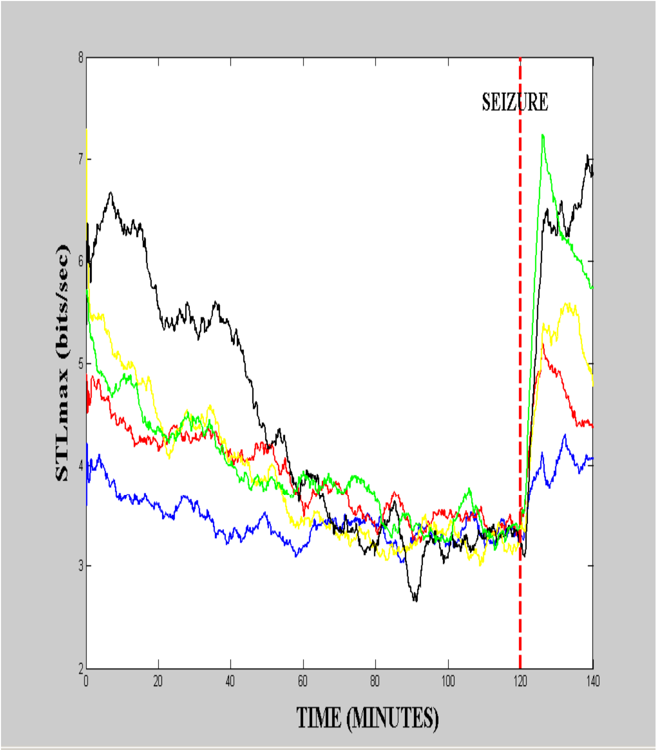
$$\dot{x} = f(x) + \varepsilon(y - y')$$
$$y = g(x)$$

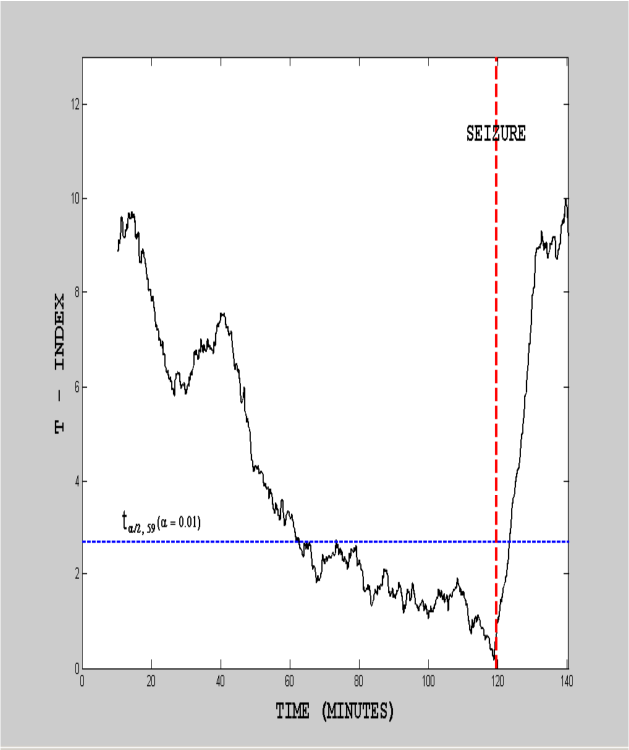
Diffusive coupling between oscillators x, x'
Increasing coupling increases synchronization
(Observer-based Stabilization)
⇒Coupling – Synchronization
⇒ Cross-talk – Synchronization

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

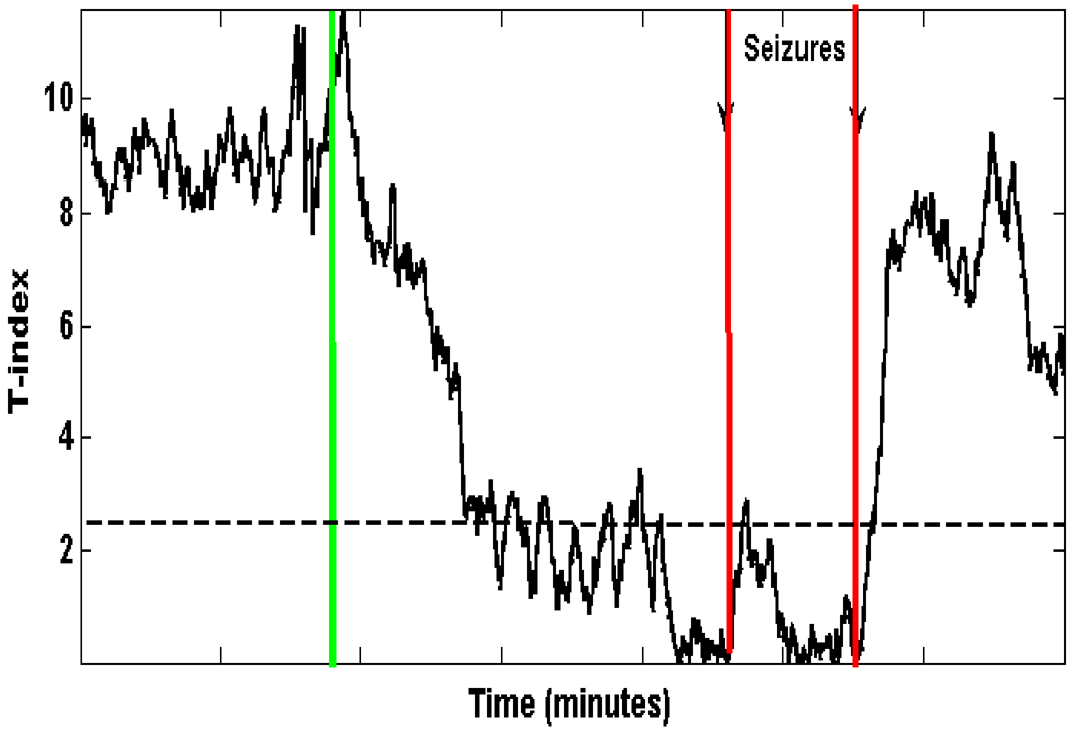
Maximum Short-term Lyapunov Exponent

STLmax and T-index profiles over time

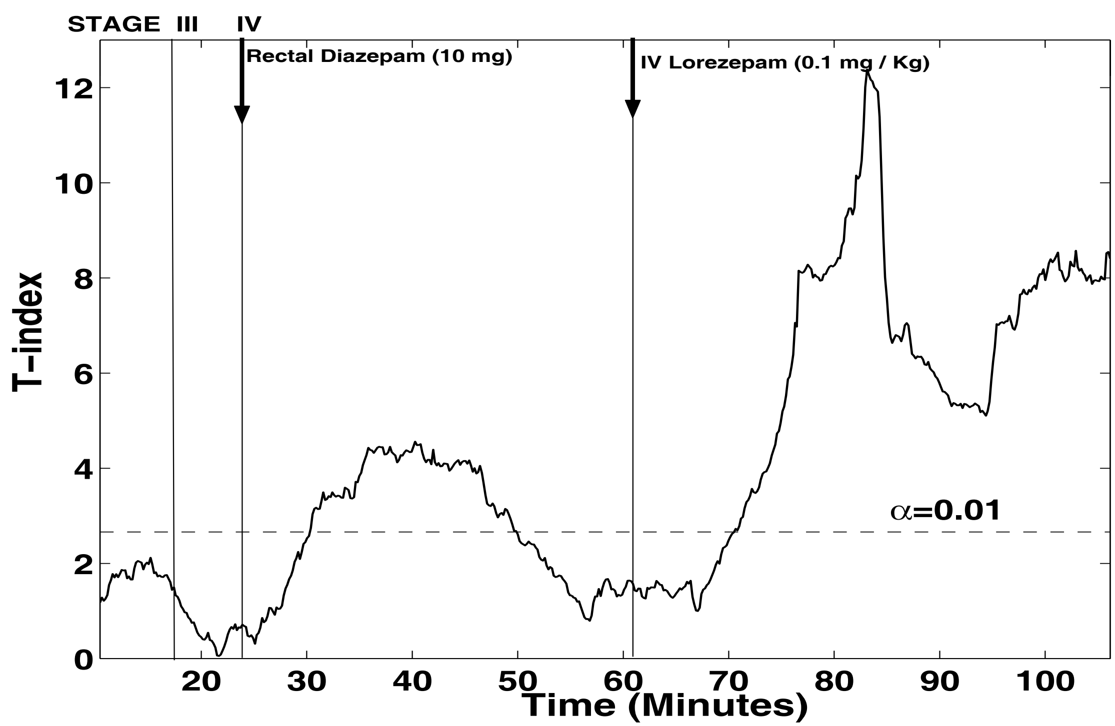




Dynamical Disentrainment: Brain Resetting by Seizures

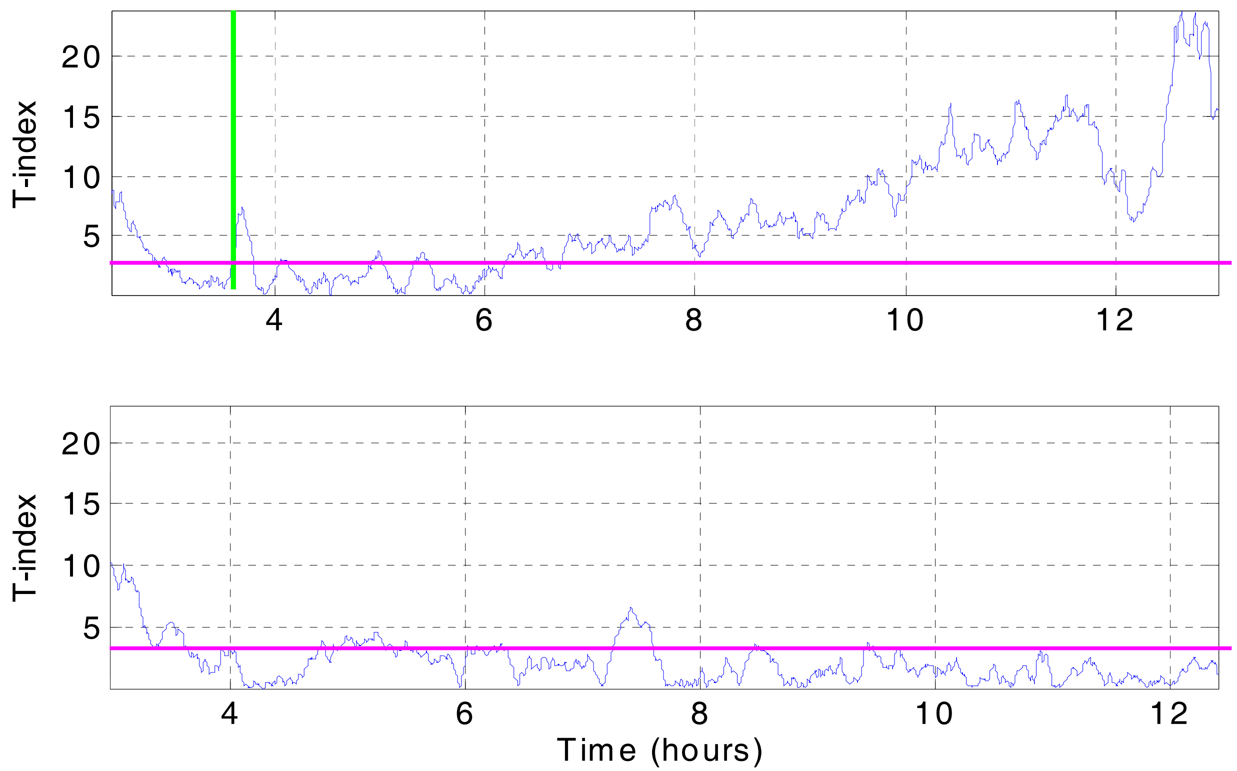


Dynamical Disentrainment: Brain Resetting by AEDs



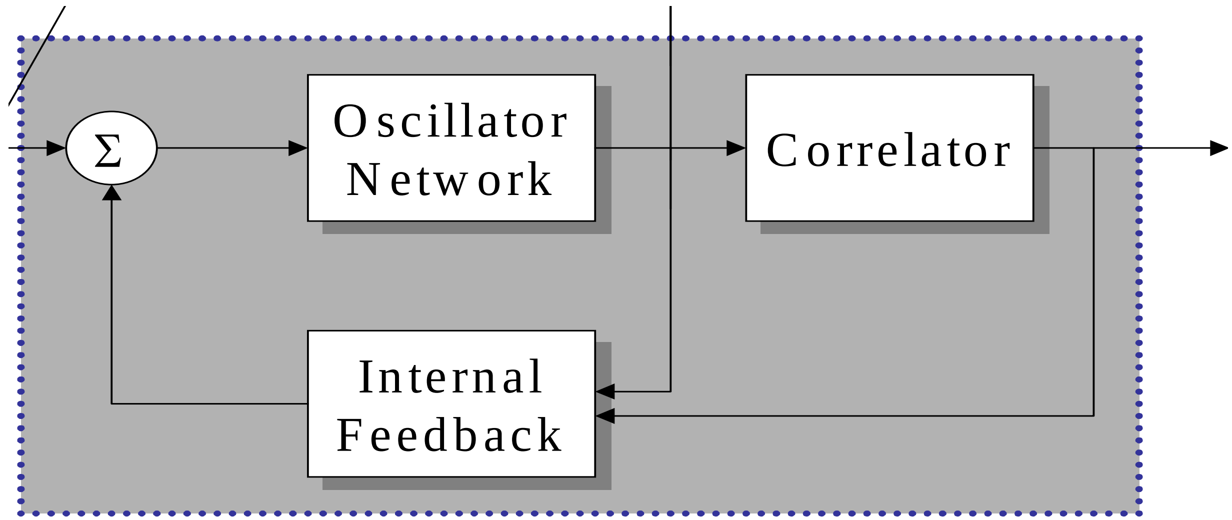
The T-index profile over time (2 HOURS) for a human status epilepticus 6-year old patient. The patient was administered 10 mg of diazepam rectally 24 minutes into the recording (end of EEG stage III), and 0.1 mg/kg of Lorezepam intravenously 61 minutes into the recording (EEG stage IV) as shown by the vertical arrows.

Dynamical Disentrainment: Brain Resetting by AEDs



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

BASIC PRINCIPLES: Control



Conjectured Functional Description of the Brain

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

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

Underlying Concepts

1. Predictable v. unpredictable seizures. Failure modes: cell/neuron-level, network-level
2. Seizures appear occasionally with normal operation most of the time (learning systems and adaptation bursting)
3. Pre-ictal increasing synchronization (increased coupling, observer feedback)
4. Primary Pathology: The epileptogenic focus acts as an attractor for the dynamics of normal sites and “attempts” to dynamically entrain normal brain sites
5. Secondary Pathology: Normal sites are not disentrained fast enough by the focus due to malfunctioning internal feedback that controls the magnitude and duration of entrainment
6. Seizures disentrain the normal sites from the focus (resetting power of seizures)

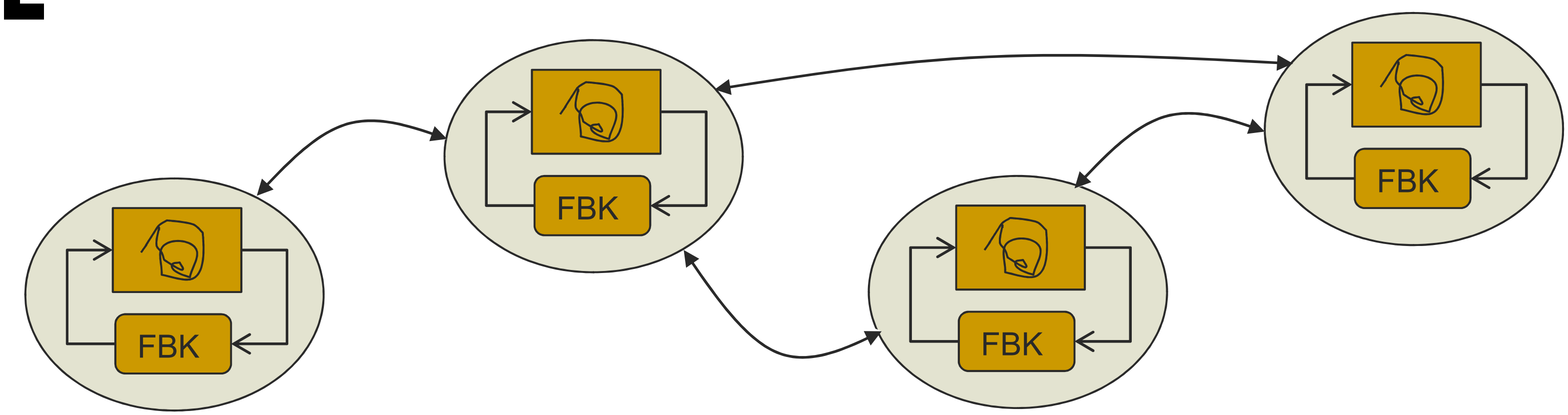
Corroborative Evidence for the Underlying Concepts

1. Dynamical Analysis of EEG
    - Type of seizures
        - Focal (Temporal Lobe; Frontal Lobe), Primary Generalized
        - Subclinical, Clinical
        - Clinical versus Electrographic seizures
        - Status Epilepticus
    - Type of electrodes
        - Intracranial
        - Scalp
2. Sources of Data
    - Patients
    - Animal models (Rodents)
    - Simulation models (coupled nonlinear oscillators, cortex, thalamus)

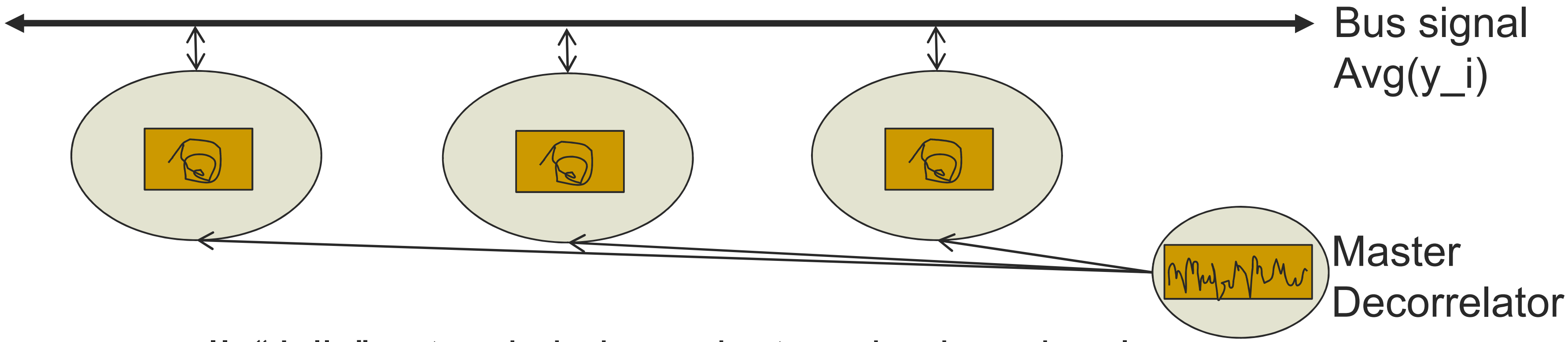
Key Observations

- 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

Model Structures



I. Evolved network, internal feedback (adaptive learning)



II. “Jello” network, independent randomizer signal

Simulation models of epileptic seizures

- Traub (SUNY Downstate, 1981- …):
  - First-principles, compartmental model of interconnected neurons, electrical current by Hodgkin-Huxley equations, 200 cells
- Freeman (Berkeley, ~1975 - …):
  - Spatio-temporal lattice of nonlinear processing elements, Emulation of basic oscillation patterns, Stochastic chaos
- Lopes da Silva, et al. (Epilepsia, 2003):
  - Semi-physical models with “intermediate level” modules
- Iasemidis et al. (Vienna, 2003; Patras, 2001):
  - Chaotic oscillators with diffusive coupling

Simulation models of epileptic seizures: interconnected chaotic oscillators

- 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

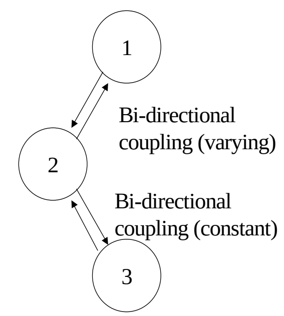
- Coupled oscillator models show synchronization but no instability

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

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

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

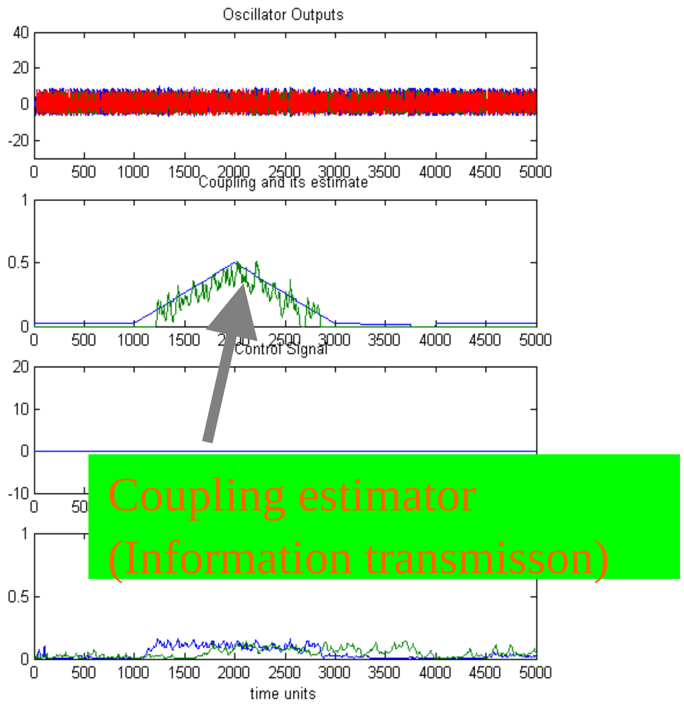
$$u^I_{ij} = k^I_{ij}(x_i - x_j), \quad k^I_{ij} = PI^I\{corr[x_i, x_j] - c^*\}$$

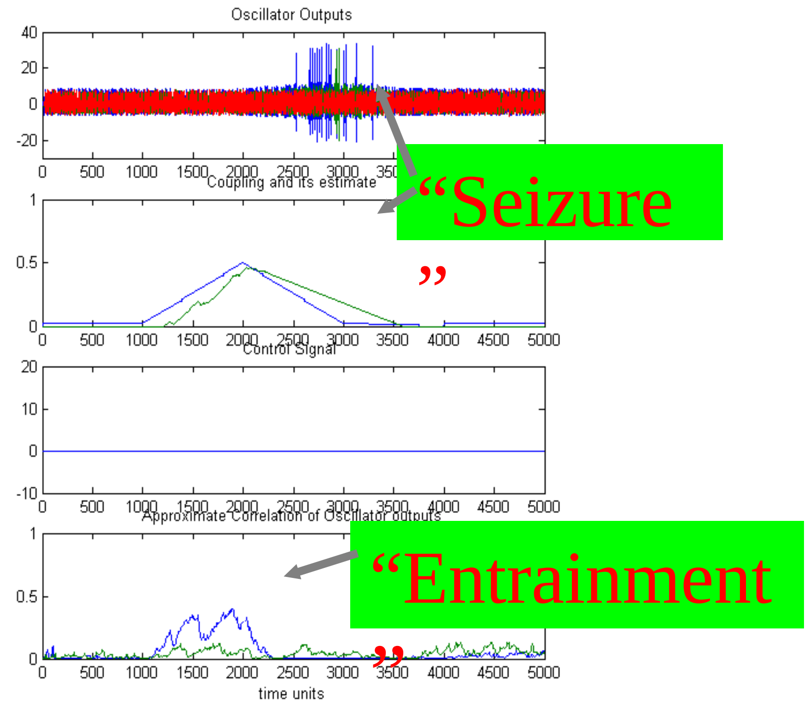


Oscillator interconnections for the MATLAB "brain emulator"

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

Model seizure details

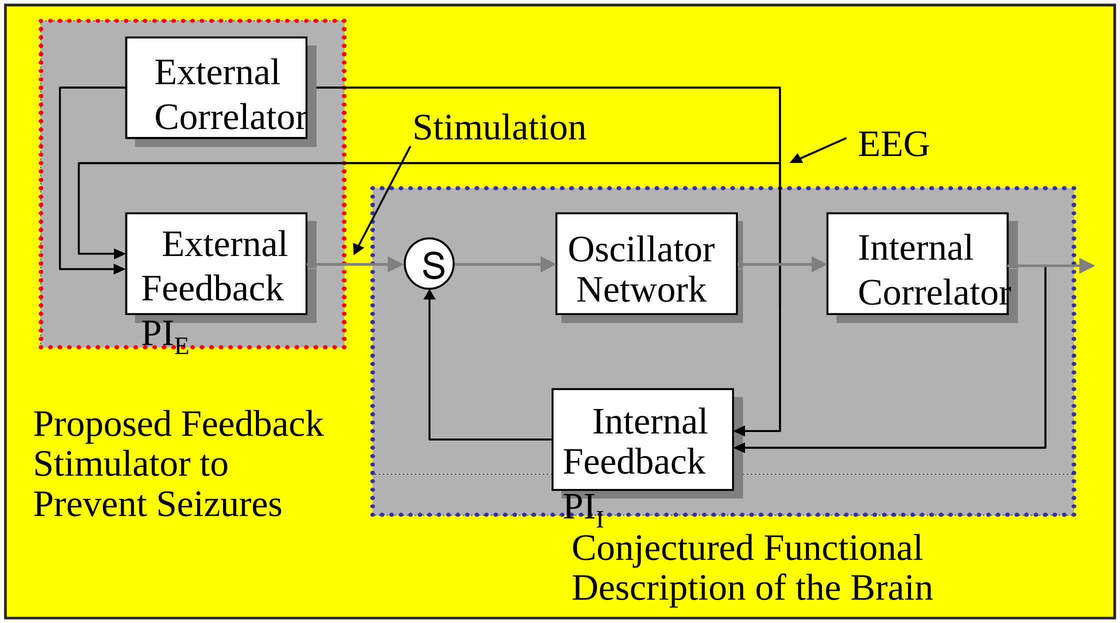




"Normal" "Epileptic"

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

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

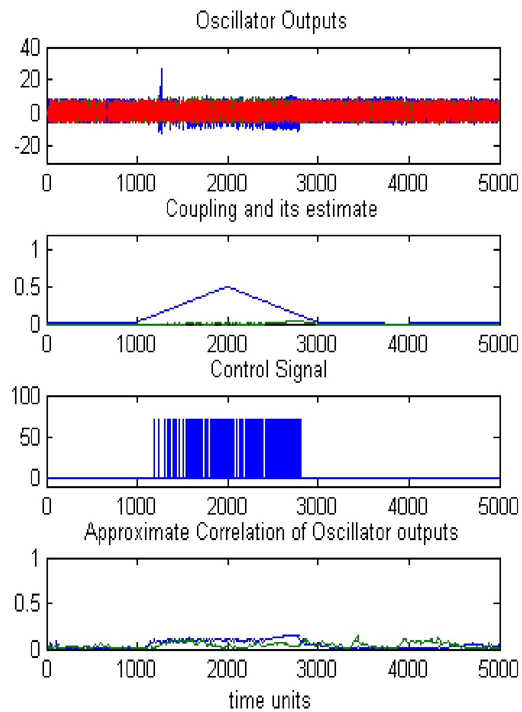
$$\frac{dy_i(t)}{dt} = \omega_i x_i + \alpha_i y_i \qquad \frac{dz_i(t)}{dt} = \beta_i x_i + z_i (x_i - \gamma_i)$$

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

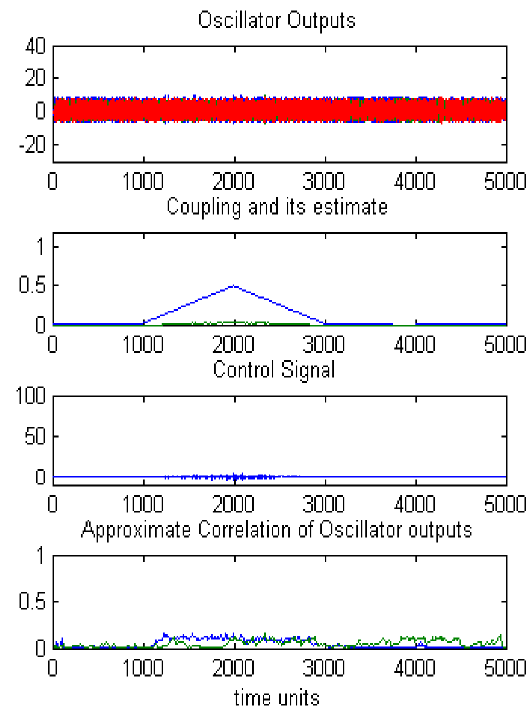
$$u_{ij}^E = k_{ij}^E (x_i - x_j), \quad k_{ij}^E = PI^E \{corr[x_i, x_j] - c^*\}$$

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

Feedback stimulation of the "Epileptic Brain"



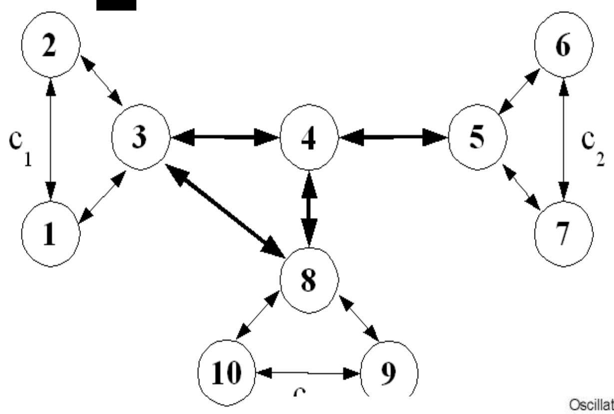
Continuous Feedback (pulses)



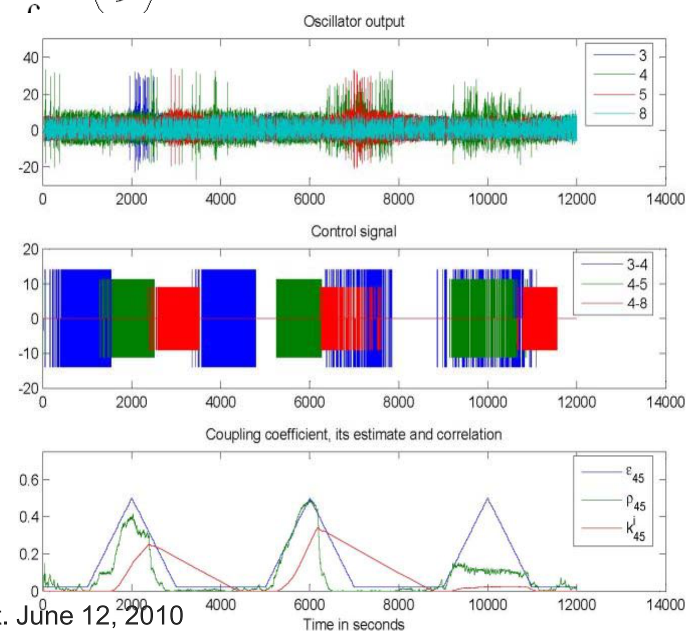
Feedback Decoupling

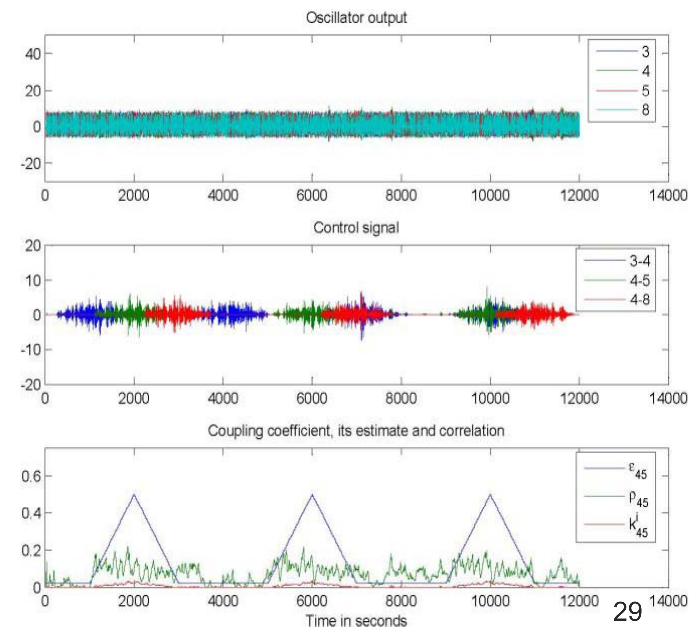
Periodic stimulation does not suppress seizures

Increasing the network complexity
Impulse-train vs. Decoupling feedback



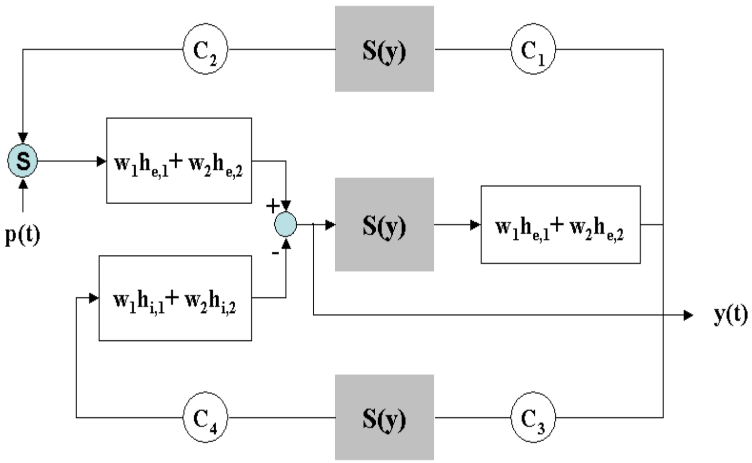
Consistent explanation of observations: failure of stimulation to suppress seizures possibly related to number of pathological connections.

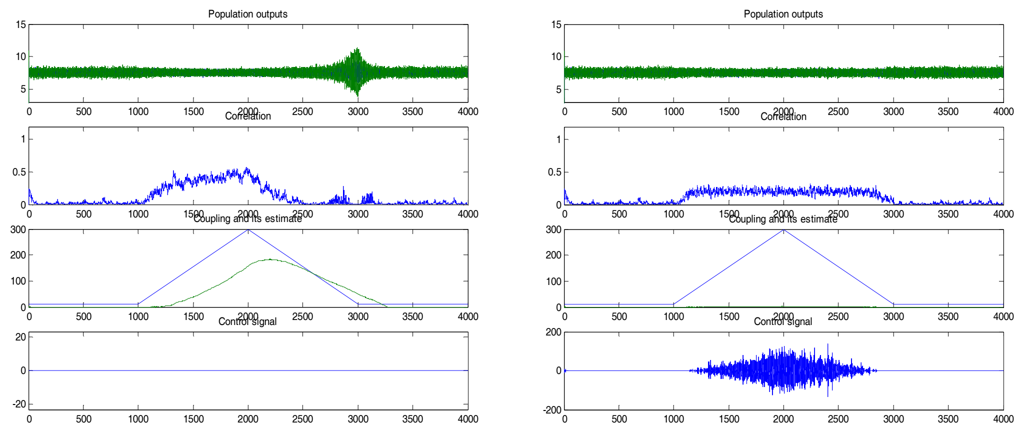




Neurophysiology-based models

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



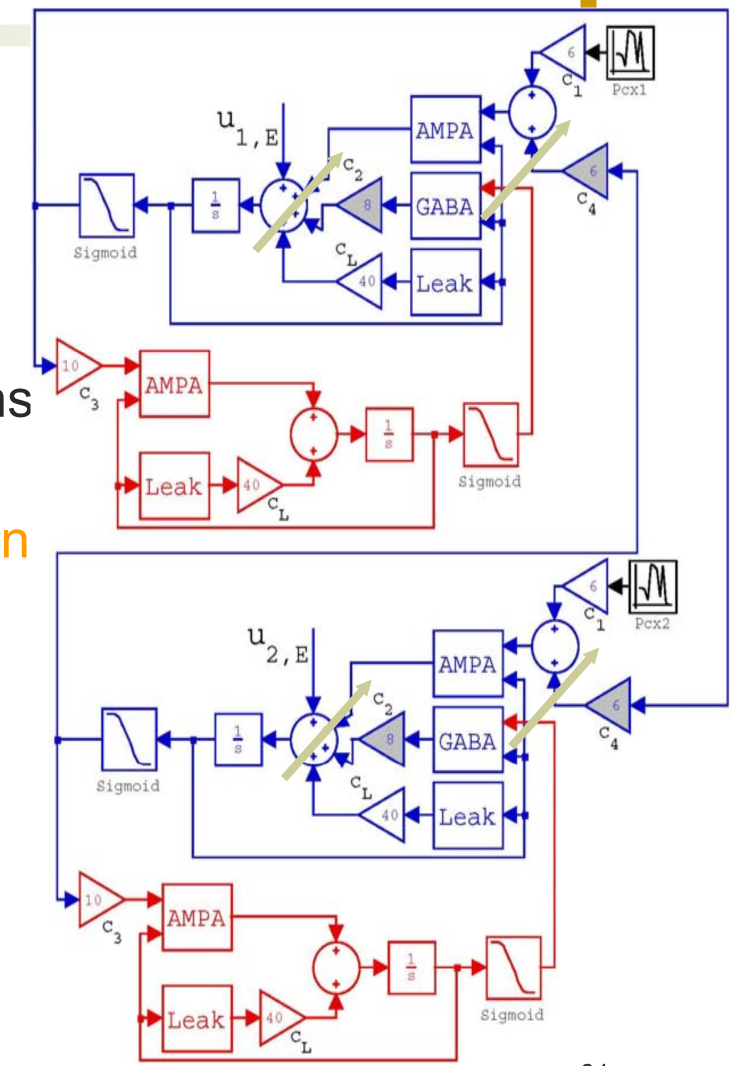


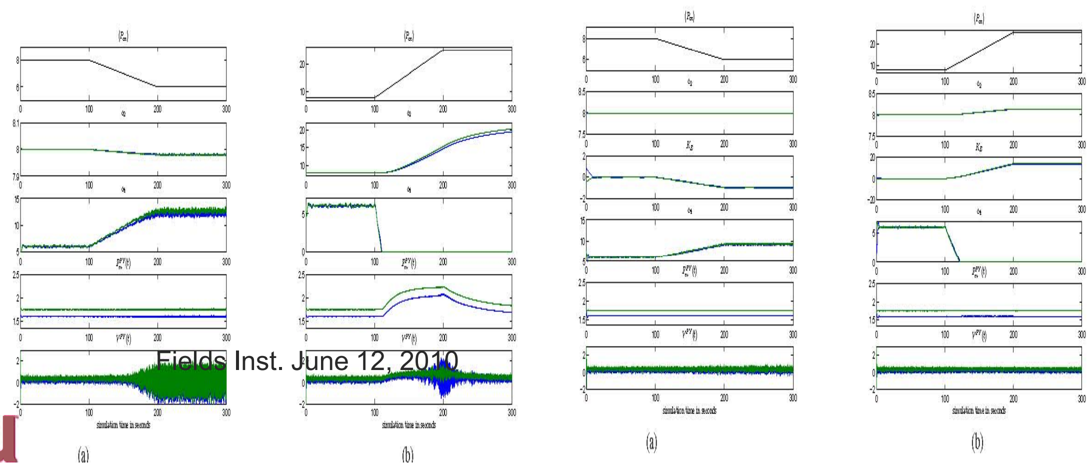
» Jansen, Zouridakis, Brandt, ``A neurophysiologically-based mathematical model of flash visual evoked potentials”, Biological Cybernetics, 68, 275-283, 1993

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

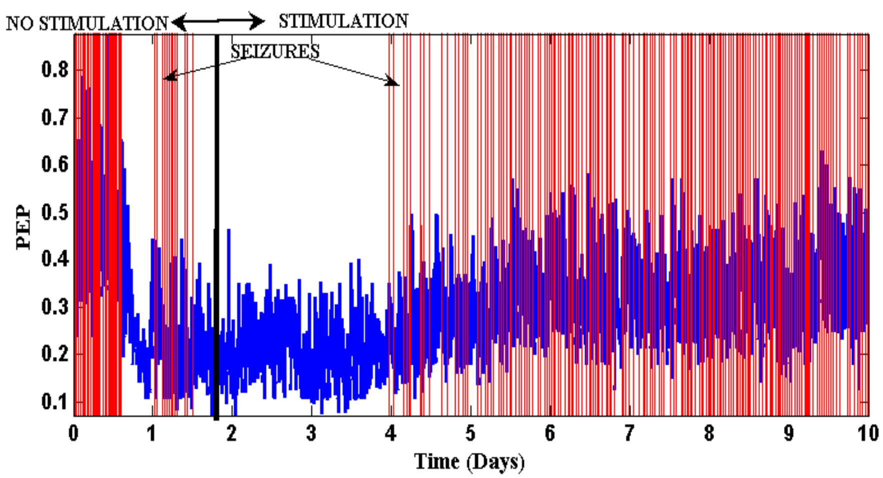
Neurophysiology-based models

- 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





Epileptic Brain Stimulation Results



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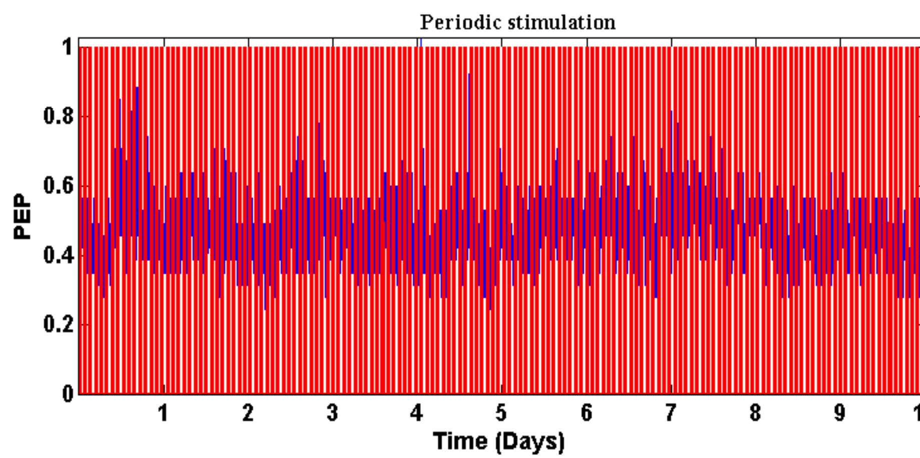
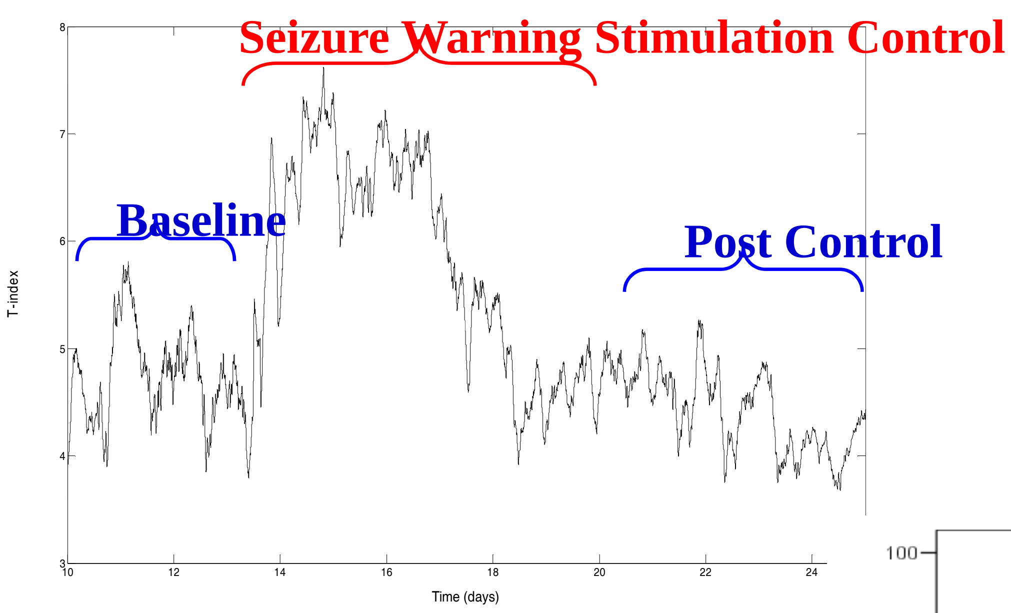


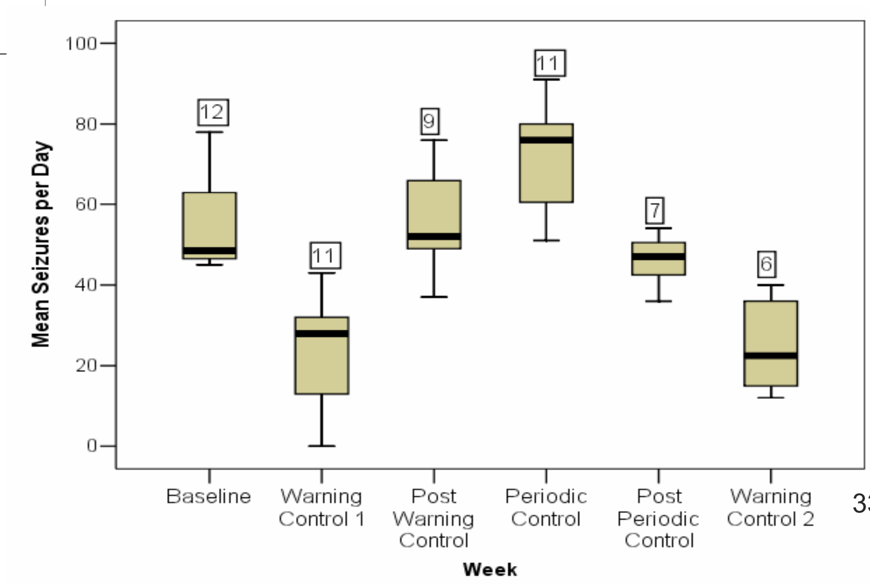
Epileptic Brain Stimulation Results



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



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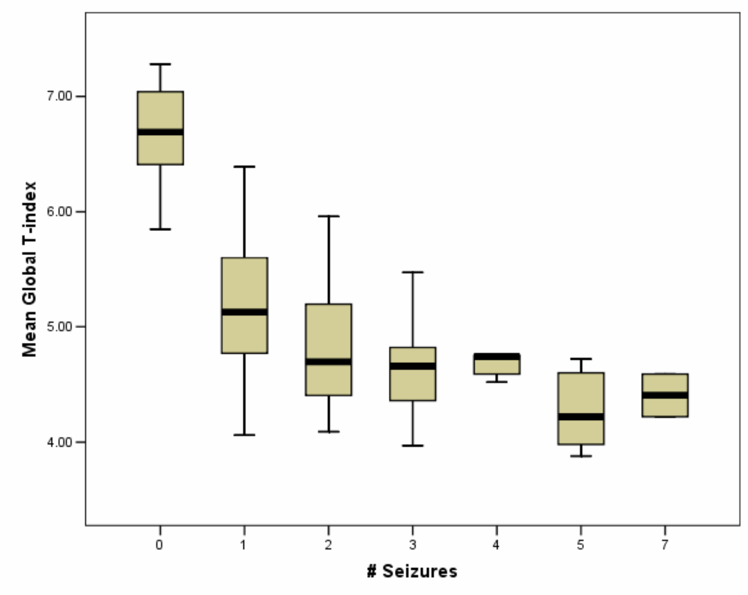
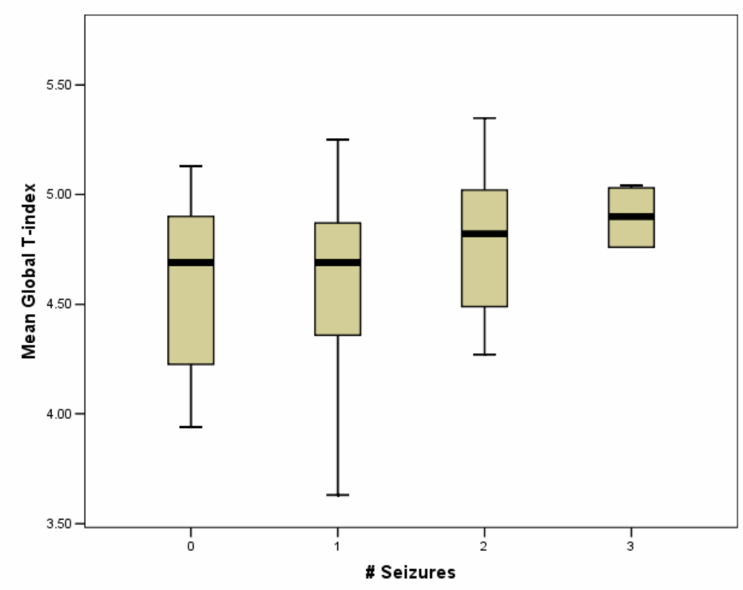


CORRELATION BETWEEN T-INDEX LEVEL AND SEIZURE FREQUENCY IN RESPONDING RATS.

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

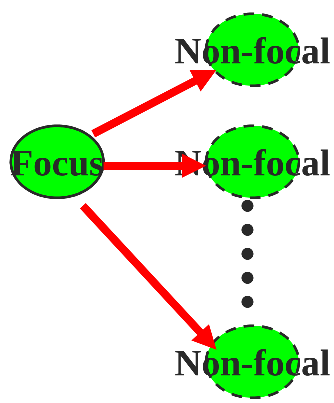


L.B. Good, S. Sabesan, S.T. Marsh, K. Tsakalis, L.D. Iasemidis & D.M. Treiman, "Automatic seizure prediction and deep brain stimulation control in epileptic rats," American Epil.Soc., 2007.

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):*

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

***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

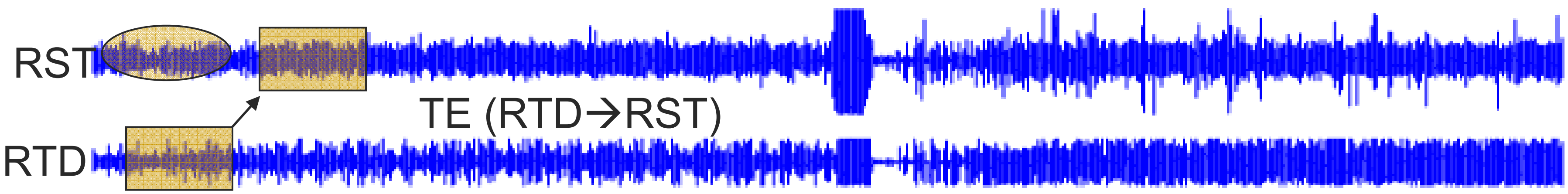
k: first minimum of mutual information

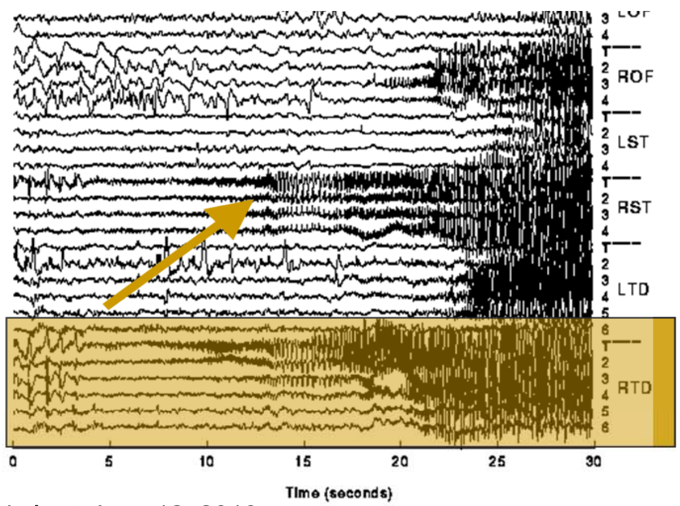
l =1; l>1 for indirect connections

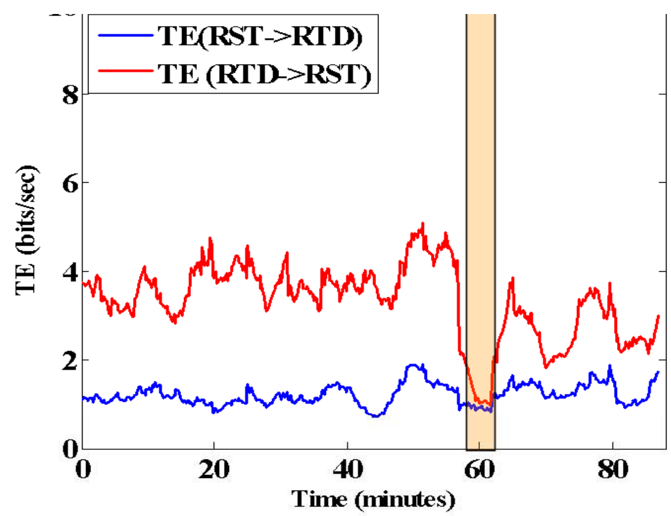
r: TE was averaged at an intermediate range of r (σ/5-2σ/5)

Transfer Entropy: Application to EEG

- *Transfer Entropy (TE): Measure of Information flow*



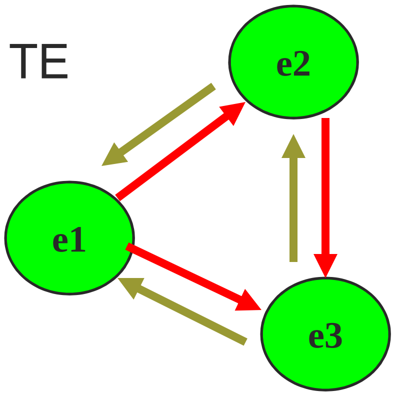




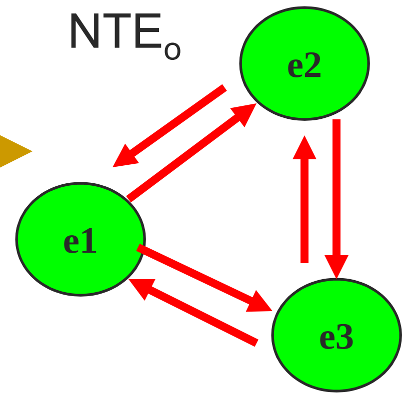
Electrical Stimulation: Focus localization

Transfer Entropy: Application to EEG

TE



NTE_o



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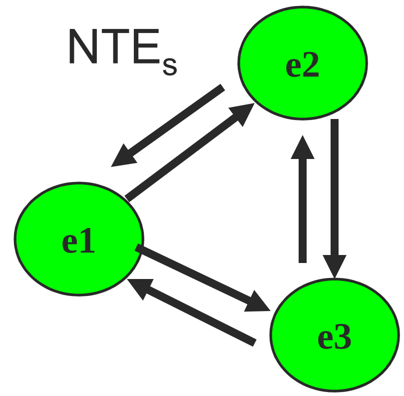
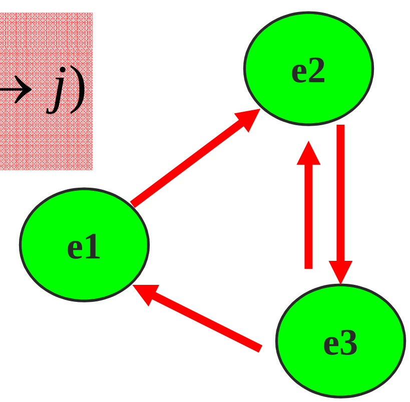
NTE_s



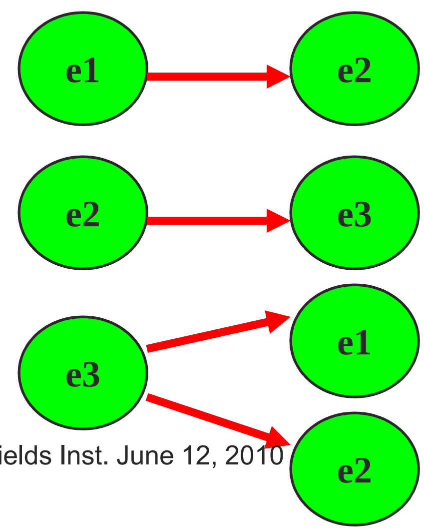
$$\frac{NTE_o^t(i\to j)-\mu\{NTE_s^t(i\to j)\}}{\sigma\{NTE_s^t(i\to j)\}} > T_{th}$$

NTE_{so}



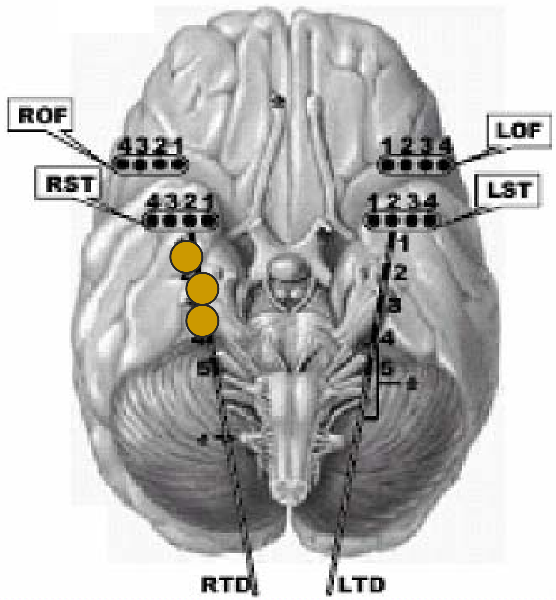
$$SANTE^t(i)=\frac{1}{N-1}\sum_{j\neq i}^{N} NTE_{so}^t(i\to j)$$

Spatially averaged NTE (SANTE)



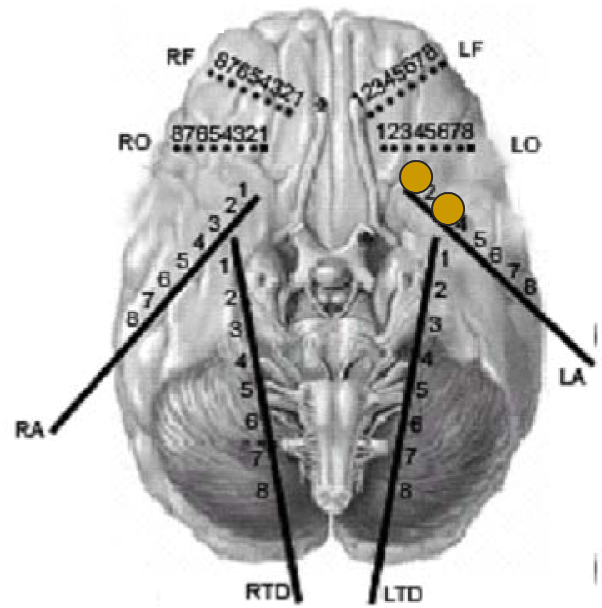
Summary of Analyzed Depth EEG data

Shands Hospital, FL



- Number of Patients Analyzed = 2
- Number of seizures = 43
- Days of recording=9.03 days/patient
- Focus: Right temporal depth (RTD)

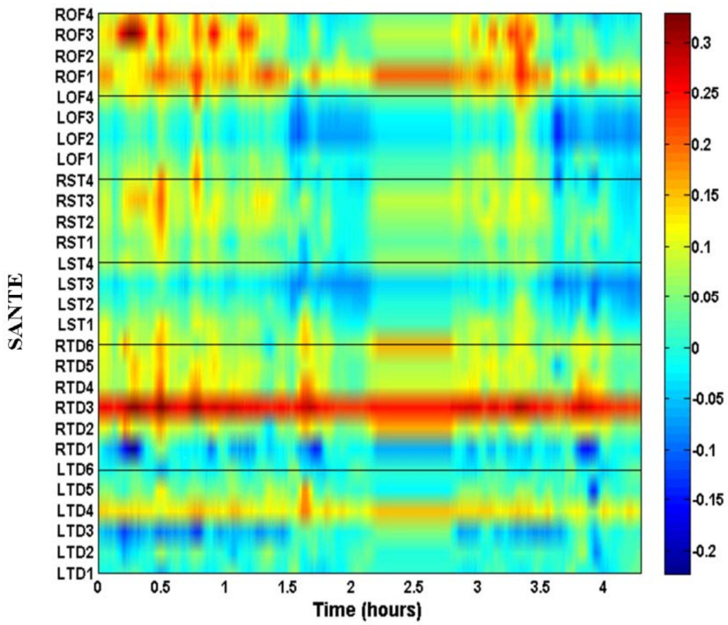
Barrow Neurological Institute, AZ



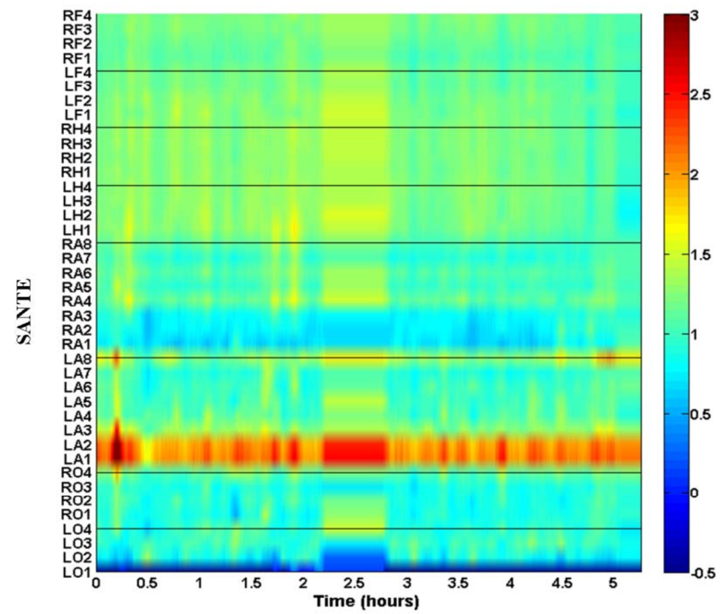
- Number of Patients Analyzed = 2
- Number of seizures=53
- Days of recording=6.16 days/patient
- Focus: Left Amygdala (LA)

SANTE over time (short-term)

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

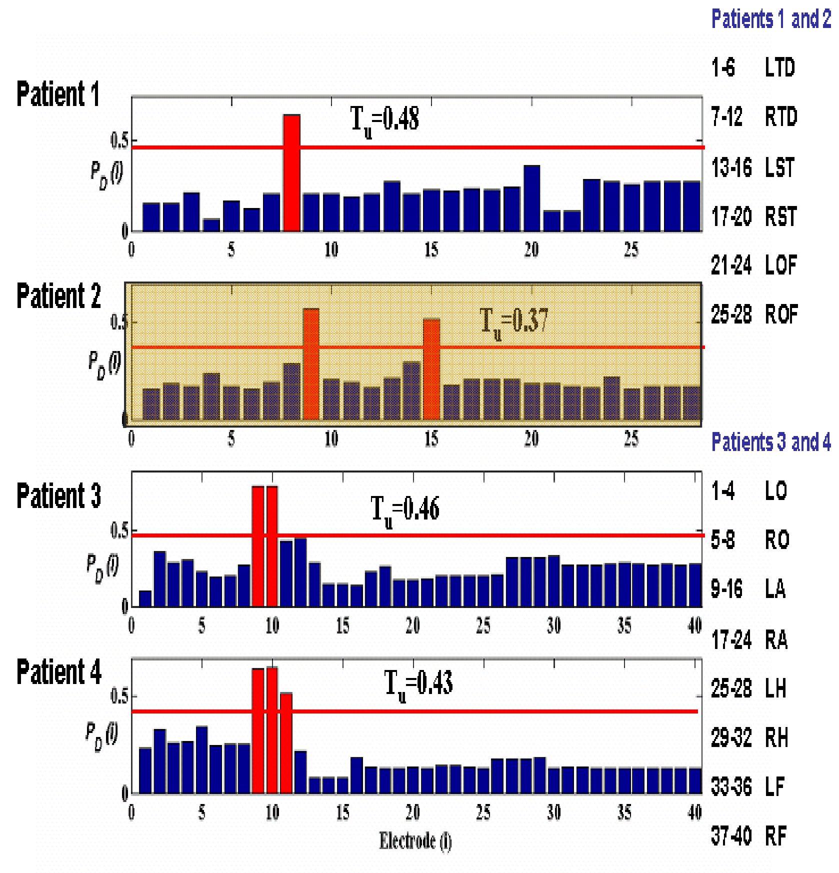
$$P(|X-\mu| \geq k\sigma) \leq \frac{1}{k^2}$$

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: Patient 2

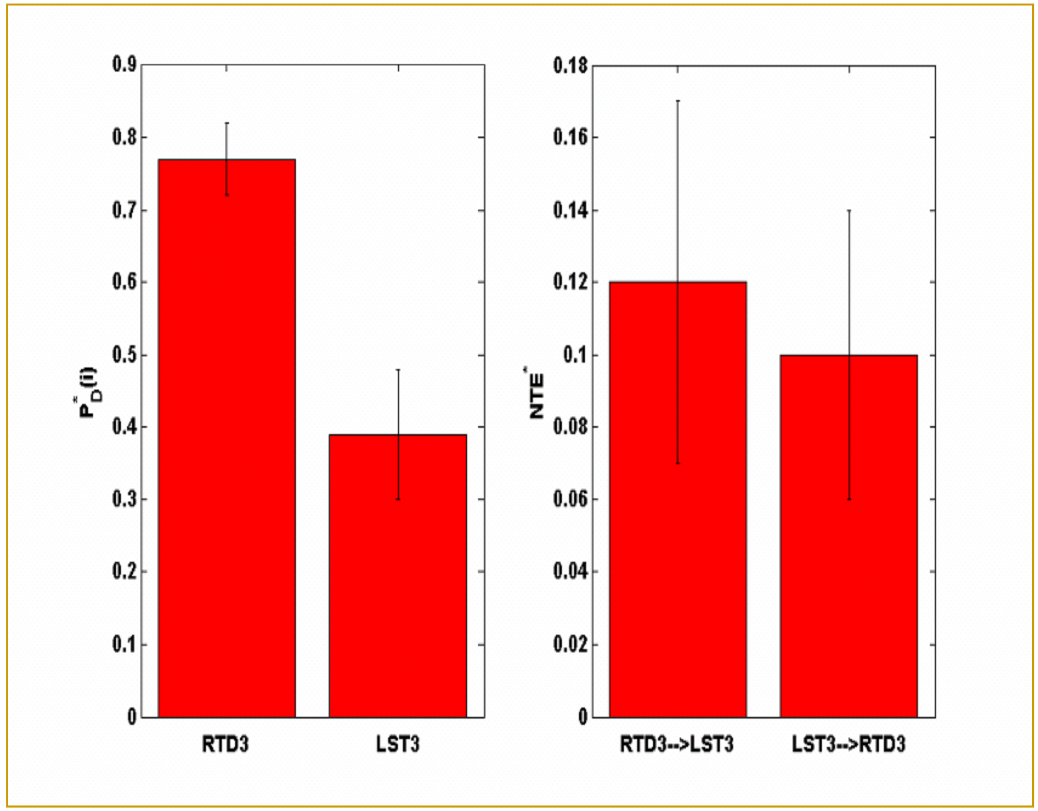
- Primary versus secondary focus ?

  Primary focal sites drive more frequently the sites residing in their own hemisphere than the ones in the contralateral hemisphere

  OR

  Two independent foci ?

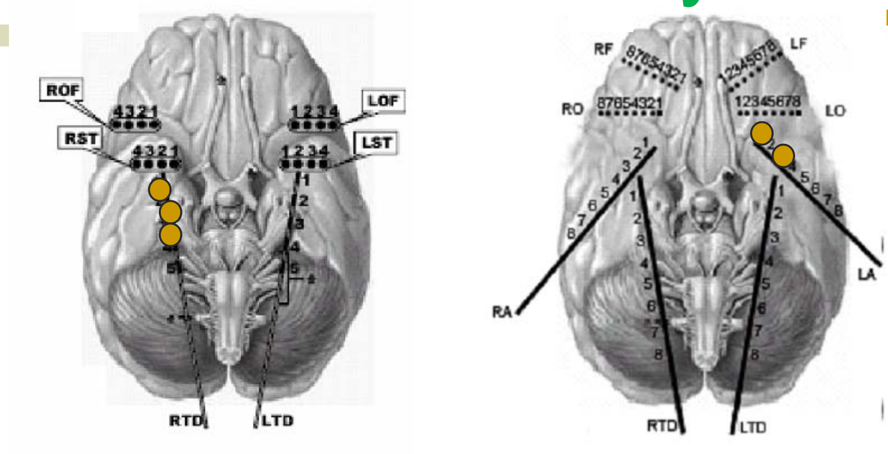
  The two focal sites drive each other equally or do not drive each other at all



P<0.001 *P*<0.6

(Mann-Whitney U test)

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)

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)
  - 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

Relevant Journal Publications

- L. Good, S. Sabesan, Steven, K. Tsakalis, D. Treiman, L.D. Iasemidis, “Control of synchronization of brain dynamics leads to control of epileptic seizures in rodents”, *Int. J. Neural Systems* , 19, 3, 2009
- S. Sabesan, L. Good, K. Tsakalis, A. Spanias, D. Treiman & L.D. Iasemidis, “Information flow and application to epileptogenic focus localization from EEG”, *IEEE Trans. Neural Systems, 17, 3, 2009.*
- N. Chakravarthy, K. Tsakalis, S. Sabesan, L.D. Iasemidis, “Homeostasis of brain dynamics in epilepsy: a feedback control systems perspective of seizures”, *Annals of Biomedical Engineering, 37, 3,* 2009.
- 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.
- 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.
- 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.
- 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.