Failing feedback as a mechanism to generate epileptic seizures

Kostas Tsakalis

Department of Electrical Engineering

Arizona State University

tsakalis@asu.edu

Credits

Collaboration

Prof. Leon Iasemidis (Harrington Dept. of Bioengineering)

Physician

Prof. David Treiman M.D. (Barrow Neurological Inst. Phoenix, AZ)

Graduate Students

Dr. Niranjan Chakravarthy

Dr. Levi Good

Shivkumar Sabesan

Support

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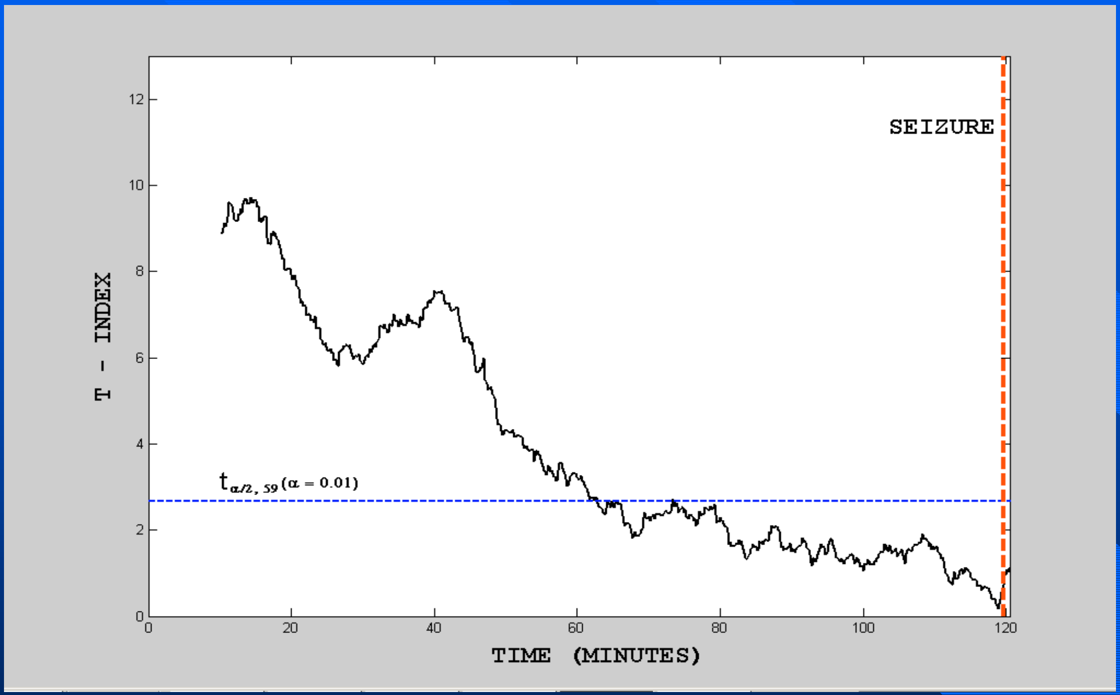
Our Problem

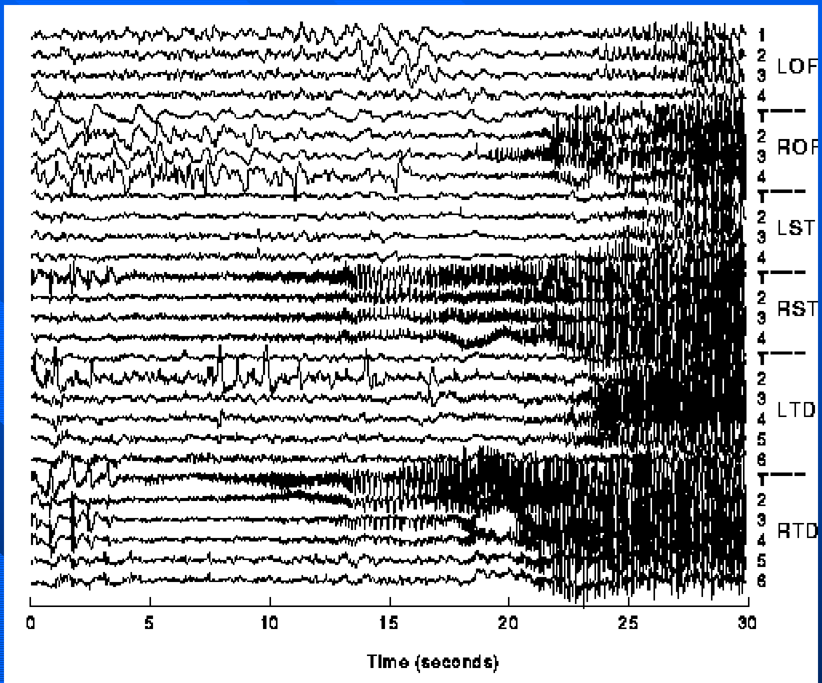
- Looking for a mechanism of seizure generation and ways to control them
- Simulation models to study funamental issues
  - coupling, entrainment (synchronization), seizures
- Design of feedback controllers for seizure suppression
  - controllability, observability
  - control objectives

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

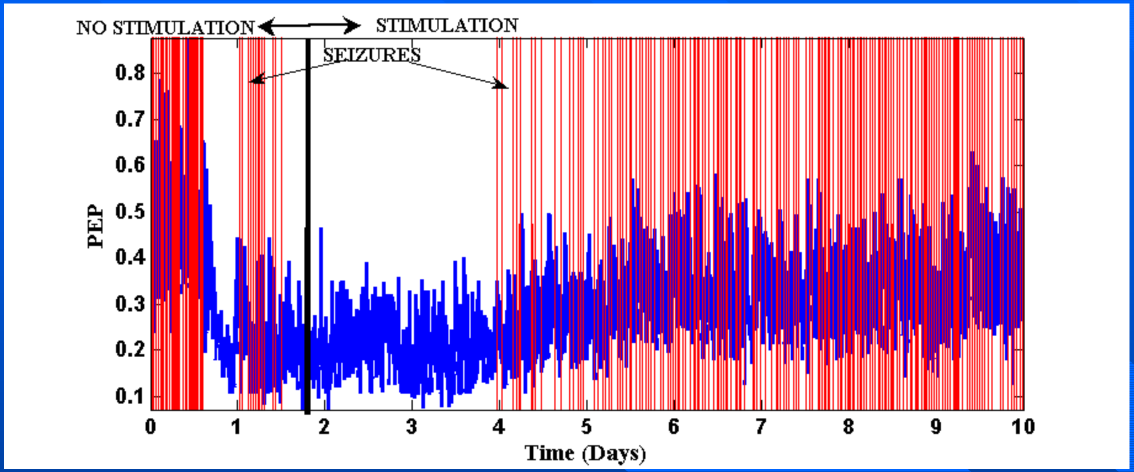




Synchronization/entrainment of brain sites indicates upcoming seizures (or, at least, susceptibility to them)

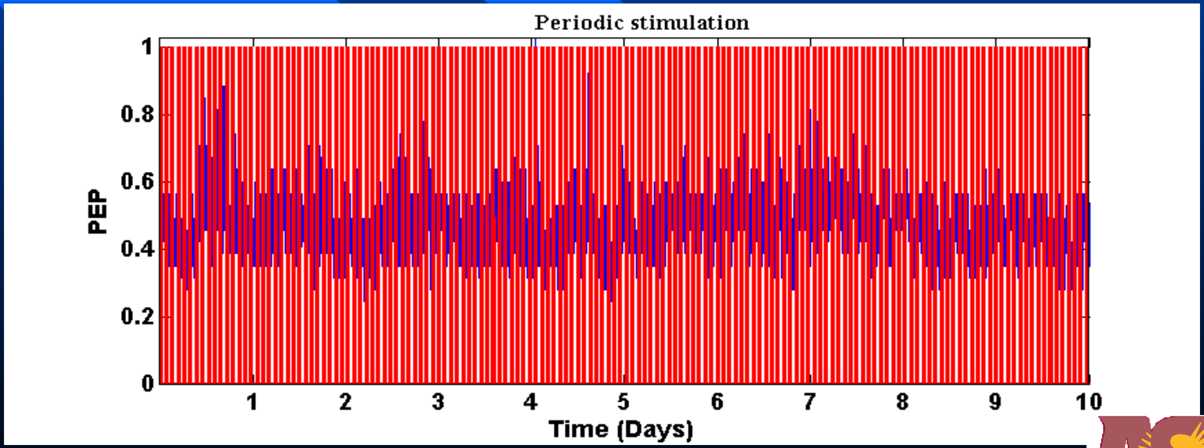
Iasemidis, 1997

Epileptic Brain Stimulation Results

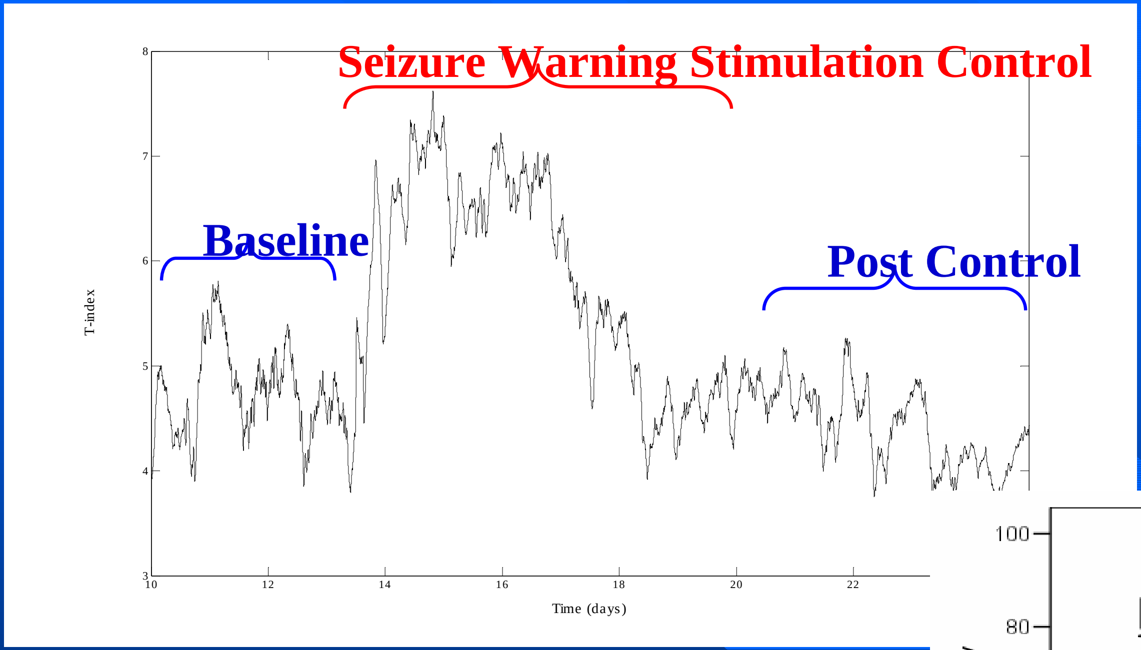


Warning–based stimulation of epileptic brain (thalamus) in rat leads to reduction of seizure frequency. But after the 4th day, the entrainment measure (PEP) increases and seizures reappear despite continuing stimulation, indicating loss of effective seizure control.

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

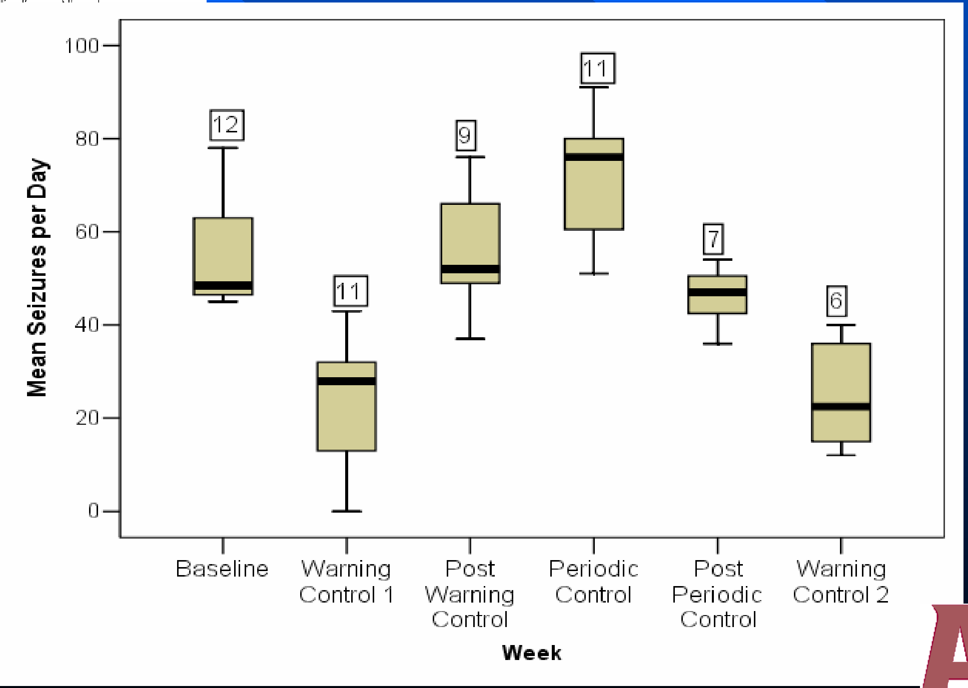


Epileptic Brain Stimulation Results



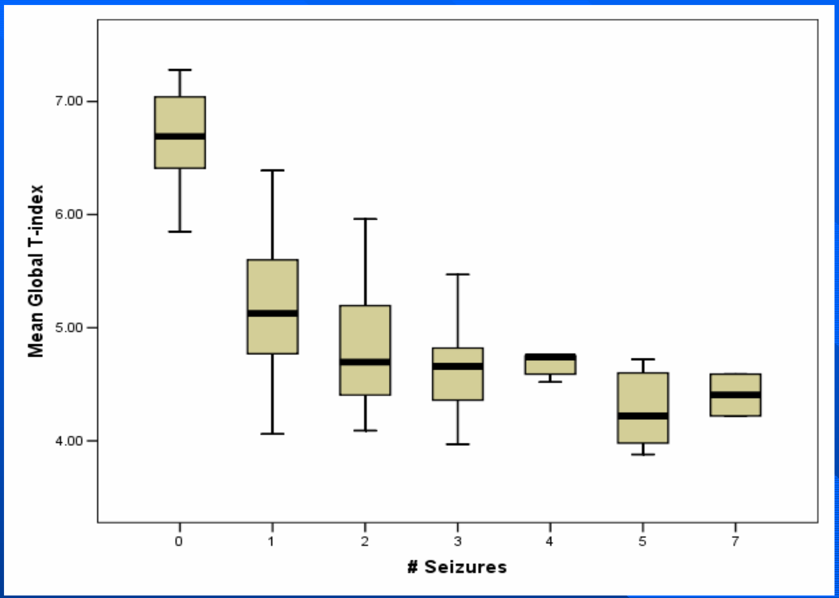
SYNCHRONIZATION DETAILS BEFORE, DURING AND AFTER CONTROL.

"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.



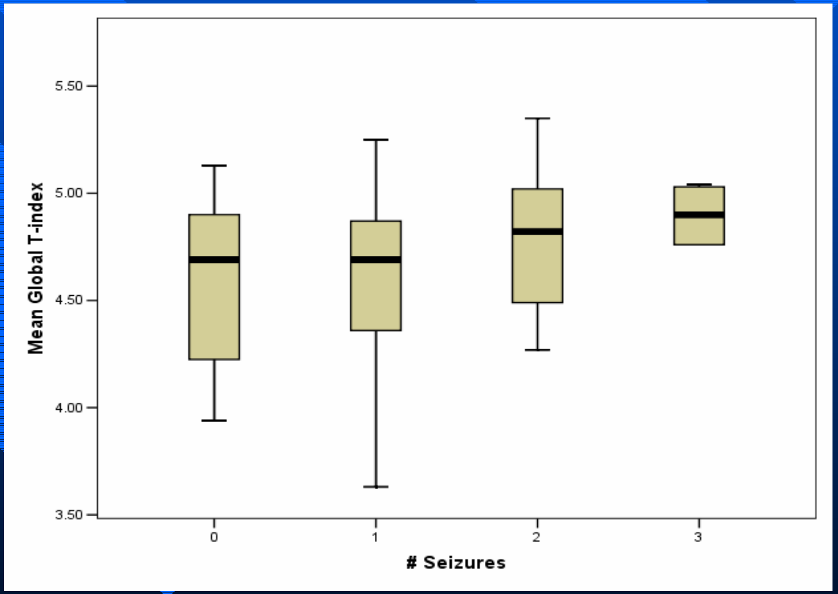
STATISTICALLY QUANTIFIED REDUCTION OF SEIZURES WITH CONTINUOUS FEEDBACK

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.

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

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

- General functional characteristics but not necessarily precise prediction
  - mechanisms of seizure generation
  - Epilepsy as a system characteristic
- Importance of interconnections (coupling)
- Feedback for homeostasis
  - with learning interpretations
- Suggestions for viable feedback control strategies

Simulation models of epileptic seizures

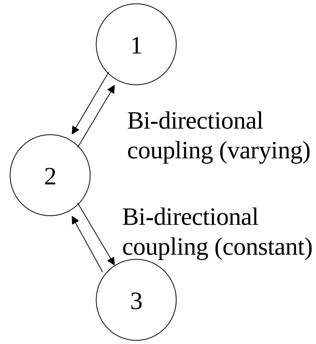
- Coupled oscillator models show synchronization but no instability

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

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

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

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

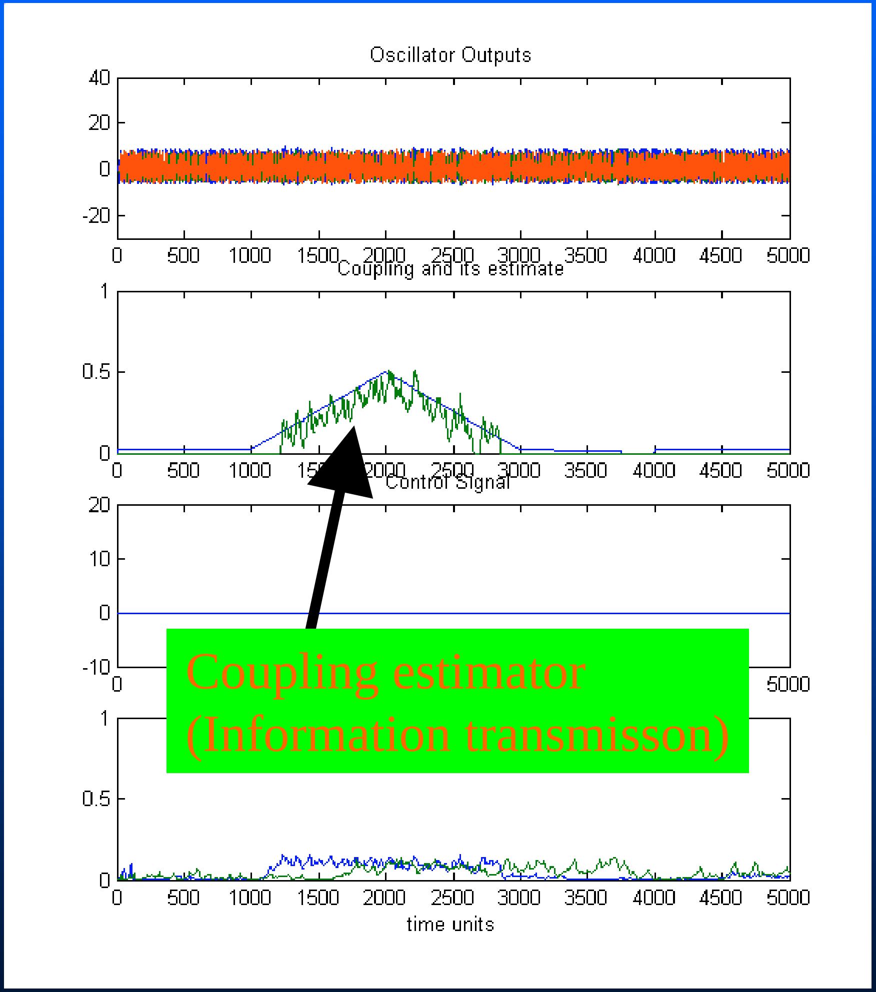


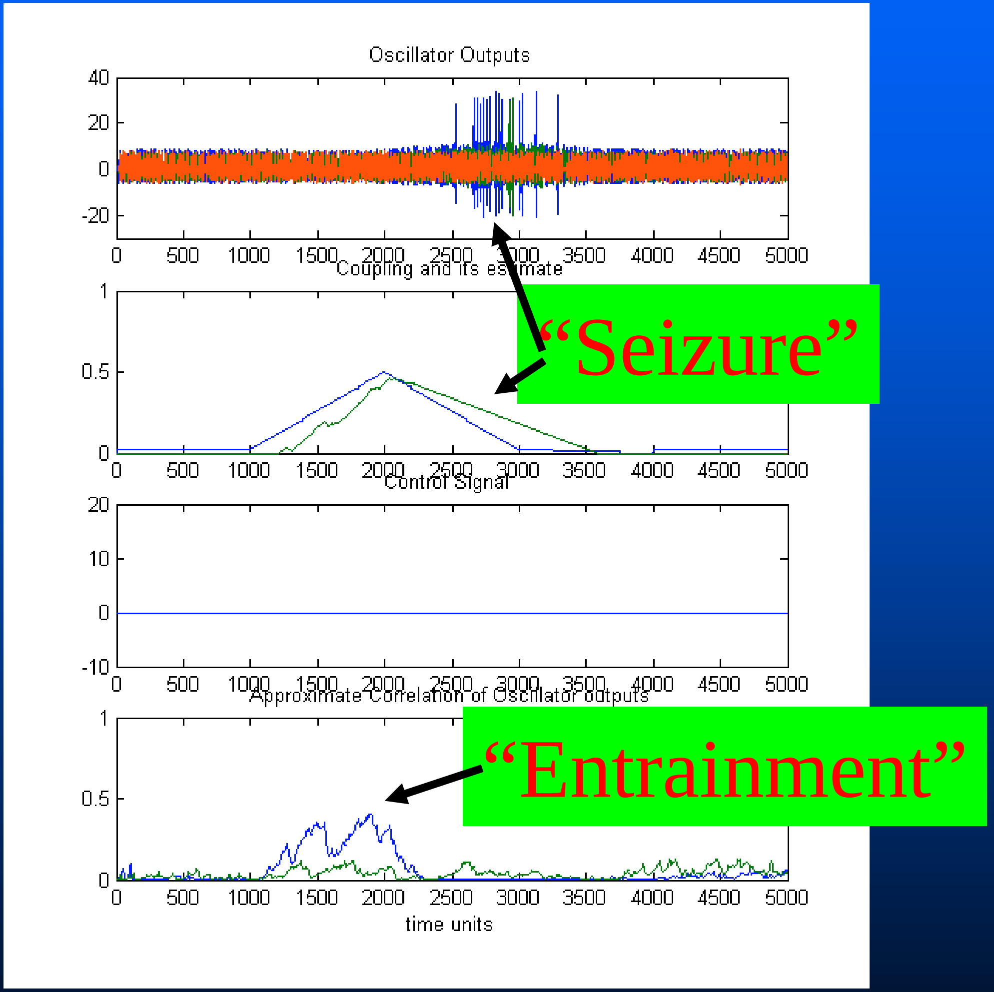
Oscillator interconnections for the MATLAB "brain emulator"

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

Tsakalis, CDC 2005

Model seizure details





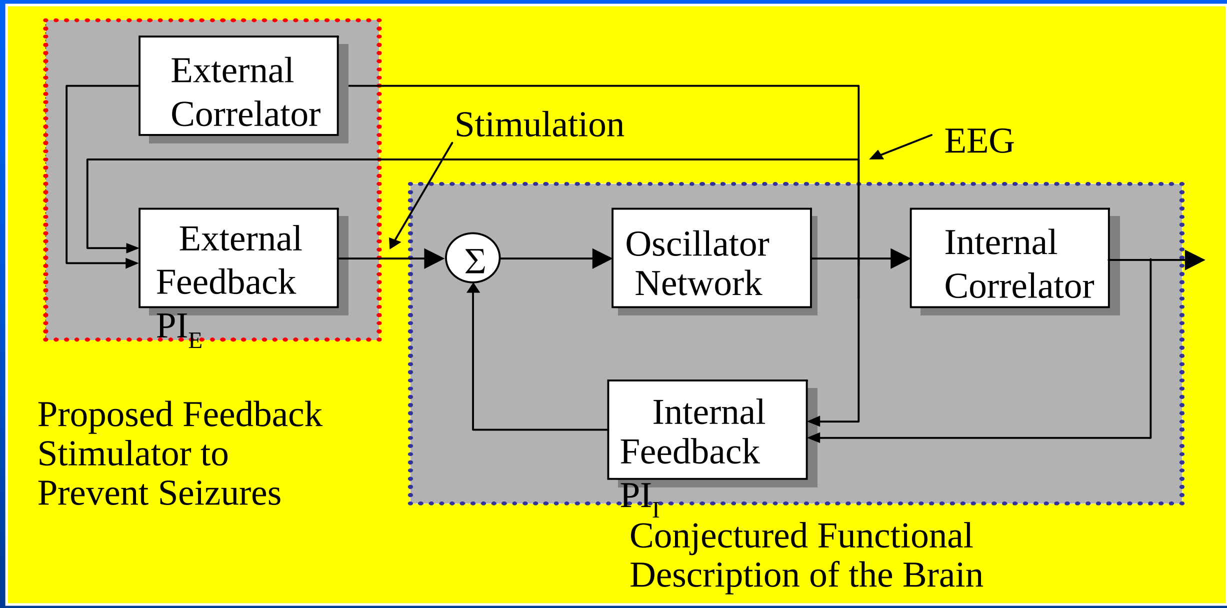
"Normal"

"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

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

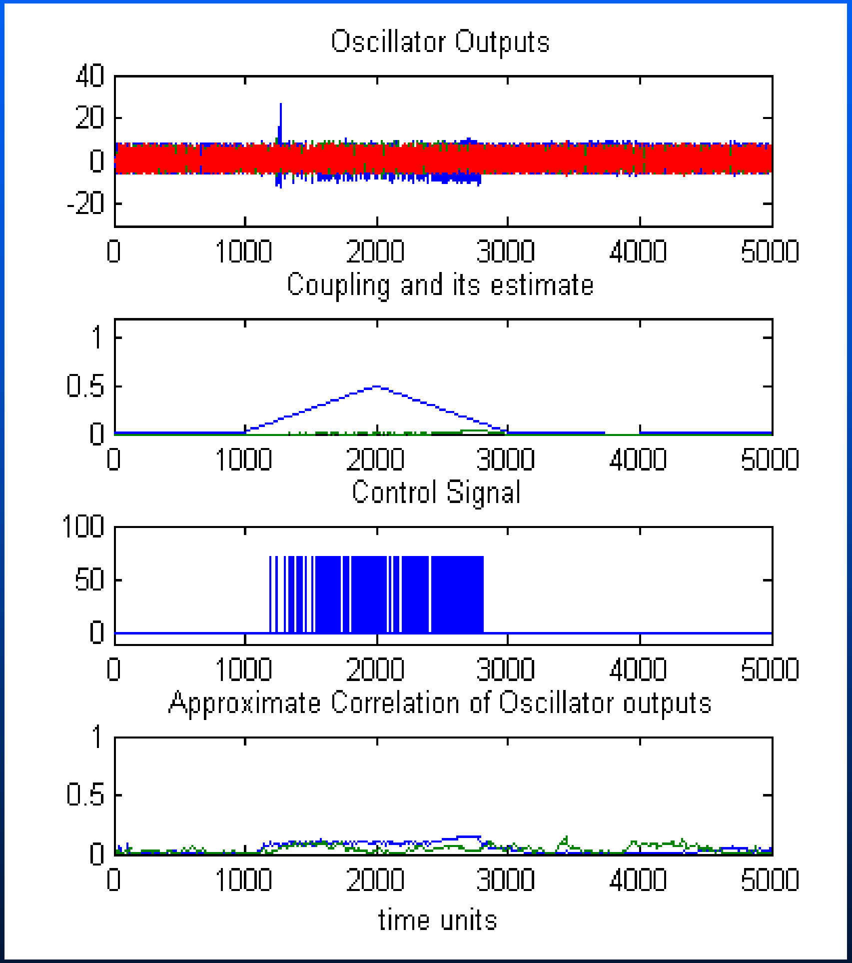
$$\frac{dy_i(t)}{dt} = \omega_i x_i + \alpha_i y_i \qquad \frac{dz_i(t)}{dt} = \beta_i x_i + z_i(x_i - \gamma_i)$$

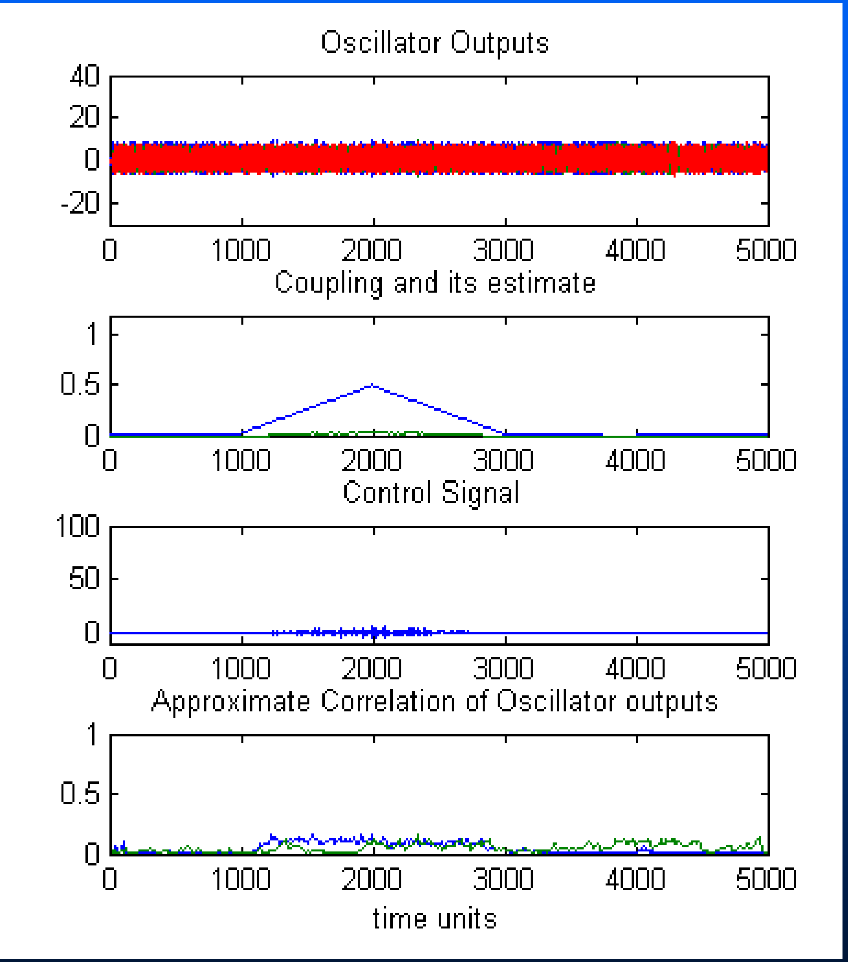
$$u_{ij}^I = k_{ij}^I (x_i - x_j), \quad k_{ij}^I = PI^I\{corr[x_i, x_j] - c^*\}$$

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

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

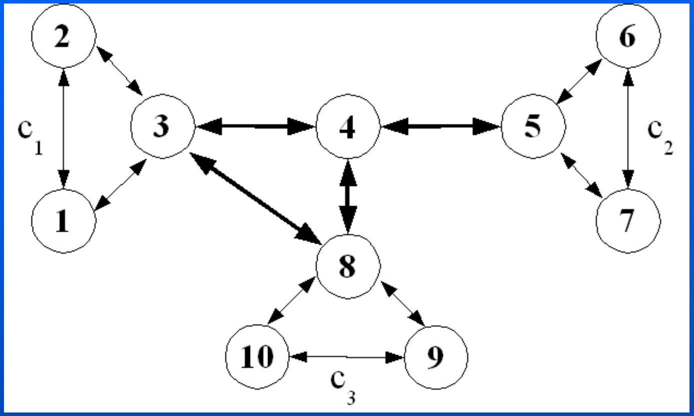
Feedback stimulation of the “Epileptic Brain”



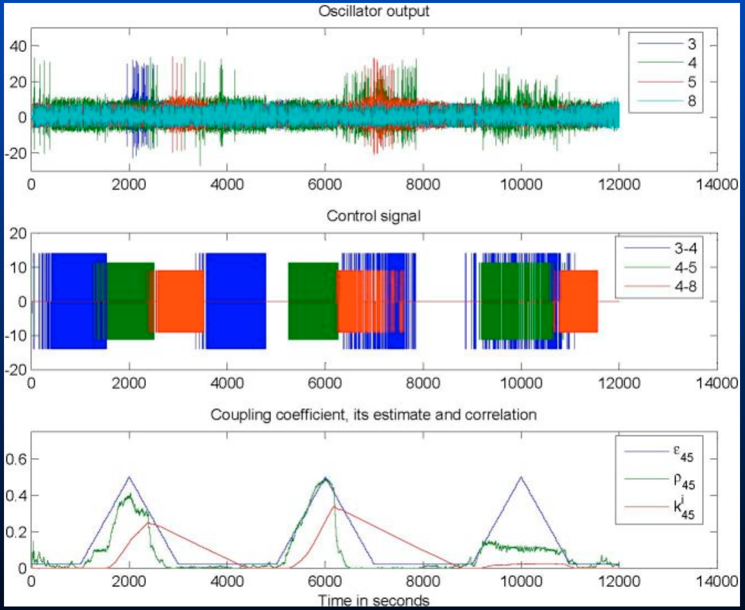


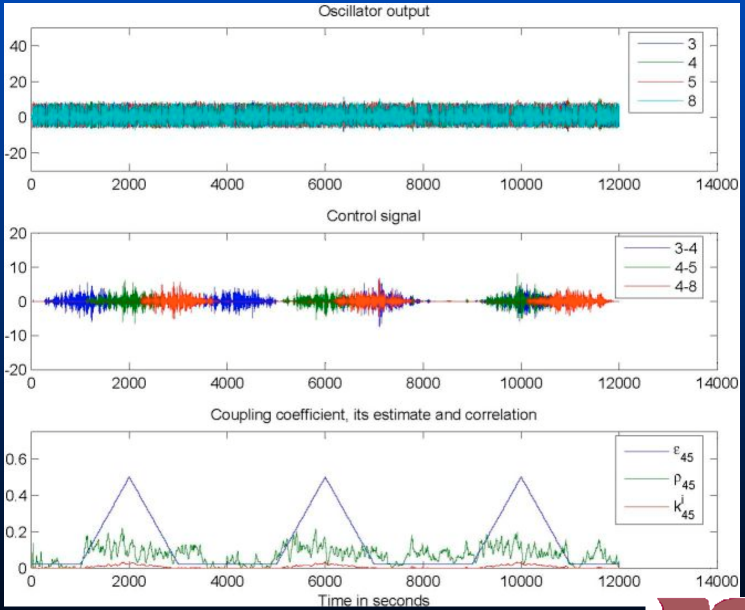
Continuous Feedback (pulses) Feedback Decoupling

Increasing the network complexity
Impulse-train vs. Decoupling feedback control



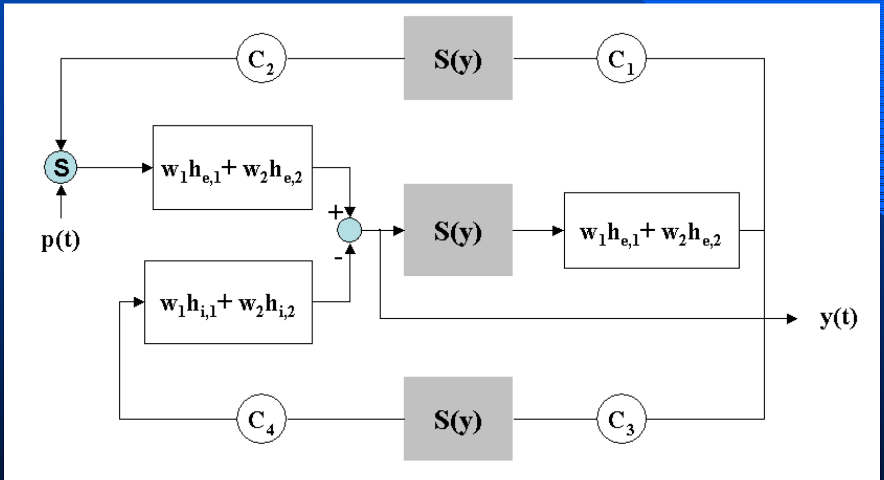
Consistent explanation of observations: failure of stimulation to suppress seizures possibly related to number of pathological connections.

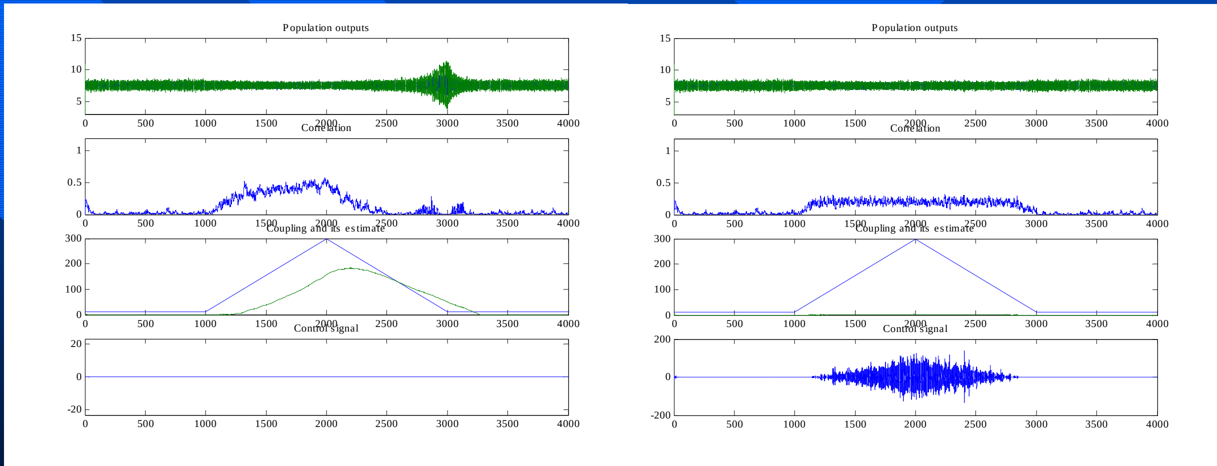




Neurophysiology-based models

- 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



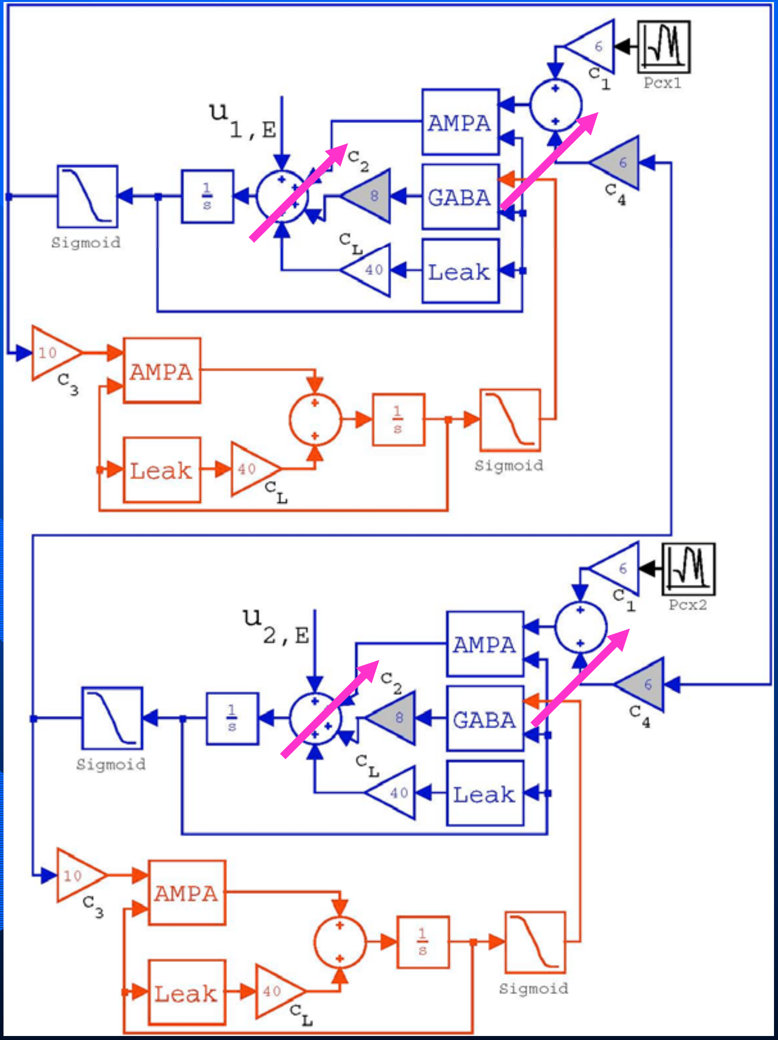


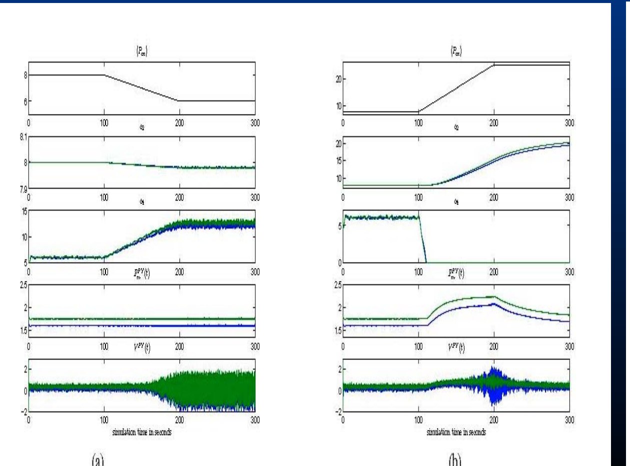
» Jansen, Zouridakis, Brandt, ``A neurophysiologically-based mathematical model of flash visual evoked potentials”, Biological Cybernetics, 68, 275-283, 1993

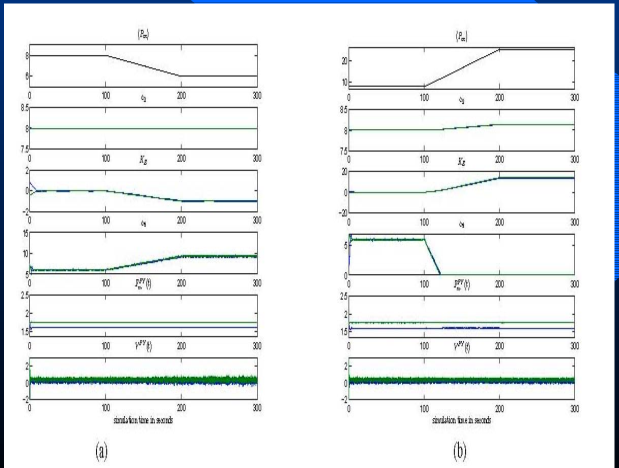
» David and Friston, ``A neural mass model for MEG/EEG: coupling and neuronal dynamics”, NeuroImage, 20, 1743-1755, 2003

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







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