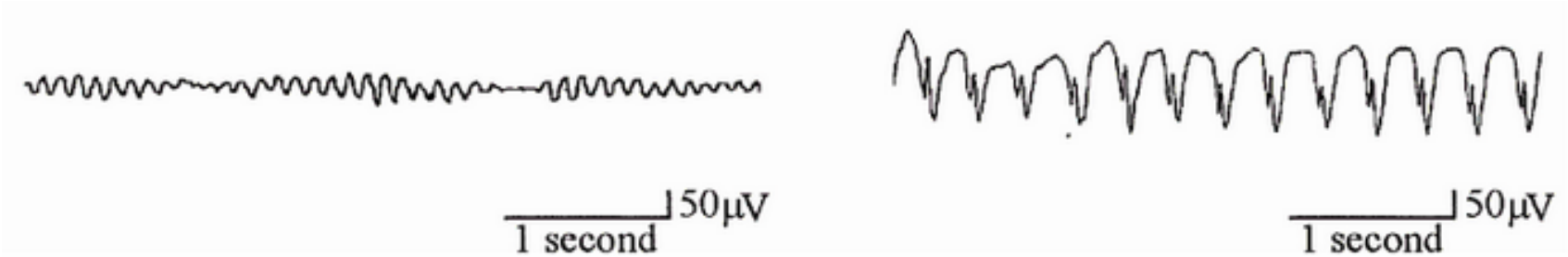
Dynamics of non-convulsive epileptic phenomena modeled by a bistable neuronal network

P. Suffczynski, S. Kalitzin, & F.H. Lopes da Silva

Neuroscience, 2004

Introduction

- neuronal networks in epilepsy possess multistable dynamics
  - normal steady state of ongoing activity
  - seizure state characterized by synchronous oscillations

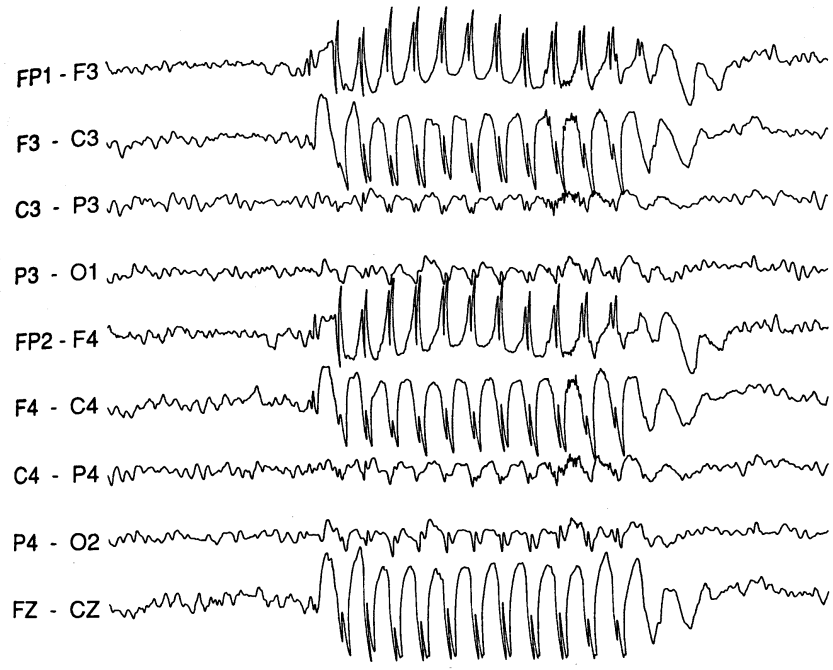


(Lopes da Silva et al, 2003)

In certain types of epilepsy, the network transitions randomly between these two states.
$\Rightarrow$ need a bistable network

Absence Seizures

- brief loss of consciousness (a few seconds to a minute)
- no warning that seizure will occur
- often induced by hyperventilization or light stimulation (may be synchronizing the brain to frequency of stimulation)
- generally diagnosed in children - many children grow out of the disorder
- mutations of $GABA_A$ receptor genes are associated with childhood absence epilepsy
- treatment by blocking low threshold Ca channels is effective in 75% of patients



State Descriptions

Normal State

- low amplitude alpha oscillations (7-14 Hz) due to reciprocal interactions between thalamocortical relay and reticular thalamic cells
- requires membrane hyperpolarization (from $GABA_A$) to deinactivate low-threshold calcium channels and produce oscillations
- called sleep spindle oscillations

Seizure State

- spike and wave (SW) discharges (seizures) of $\sim$3 Hz and large amplitude
- slower timescale $GABA_B$ receptors necessary for seizures
- blockage of $GABA_A$ receptors transforms normal state oscillations into slow large amplitude oscillations

Bistable Neuronal Network

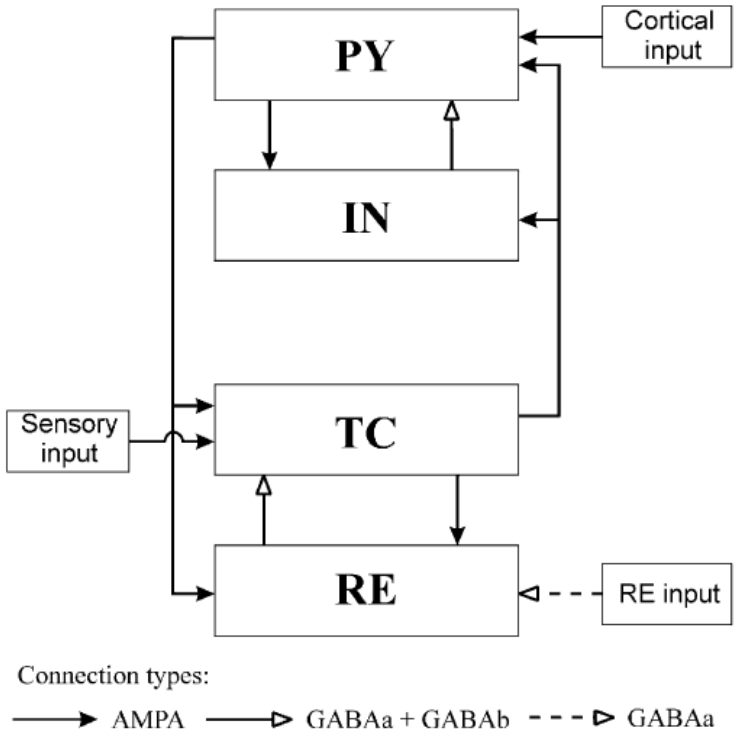
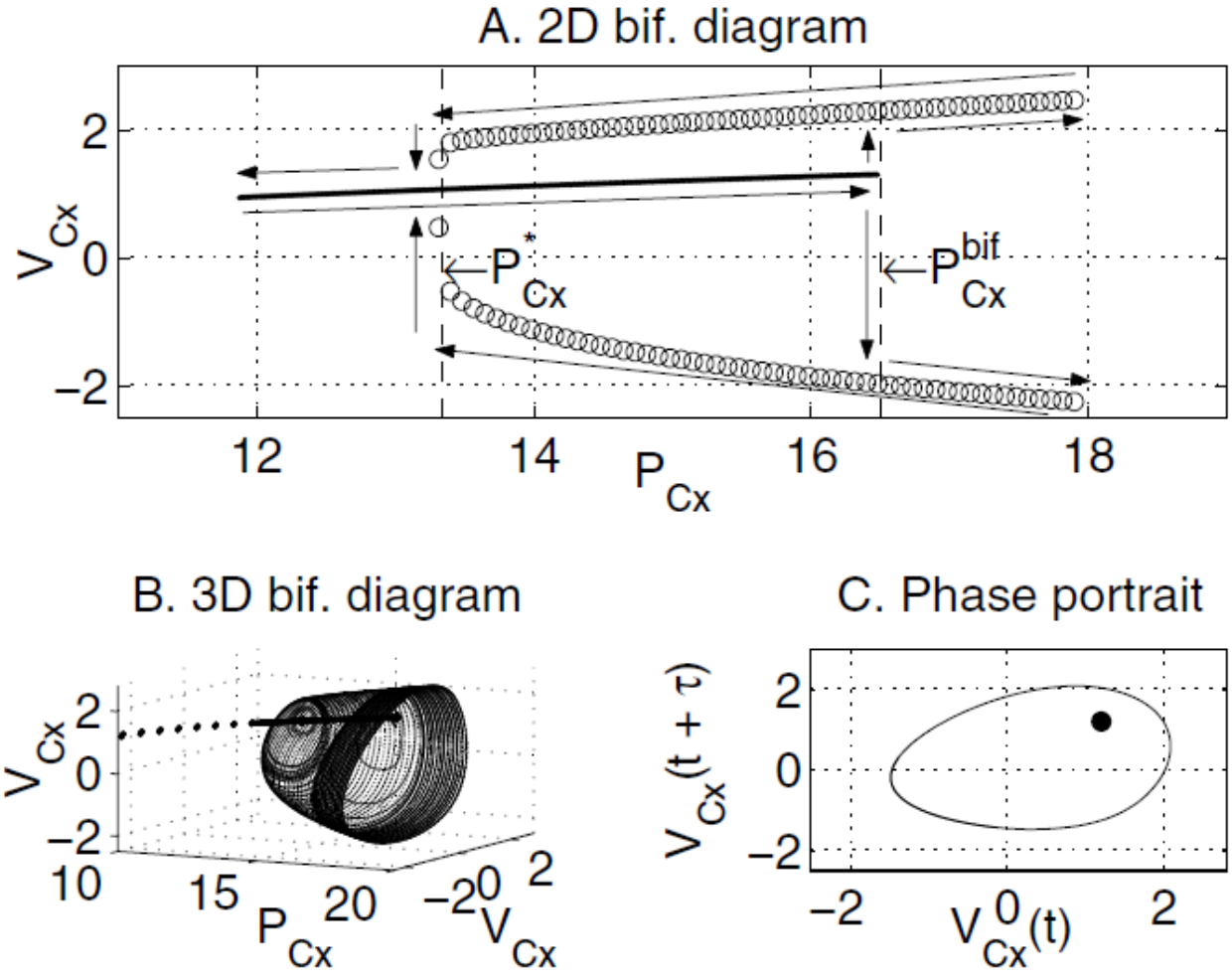


Fig. 1. Schematic structure of connections in the thalamo-cortical network model consisting of cortical and thalamic modules. The cortical module consists of two interconnected populations of PY and IN neurons. The thalamic module consists of two interconnected populations of the TC and RE neurons. TC cells project to both the PY and IN cells, while PY cells project to both the TC and RE cells. The PY population receives external cortical excitatory input, the TC population receives external sensory input and the RE population receives external inhibitory input. Figure's legend shows synaptic connection types.

PY = pyramidal cells
IN = cortical interneurons
TC = thalamocortical neurons
RE = reticular thalamic cells

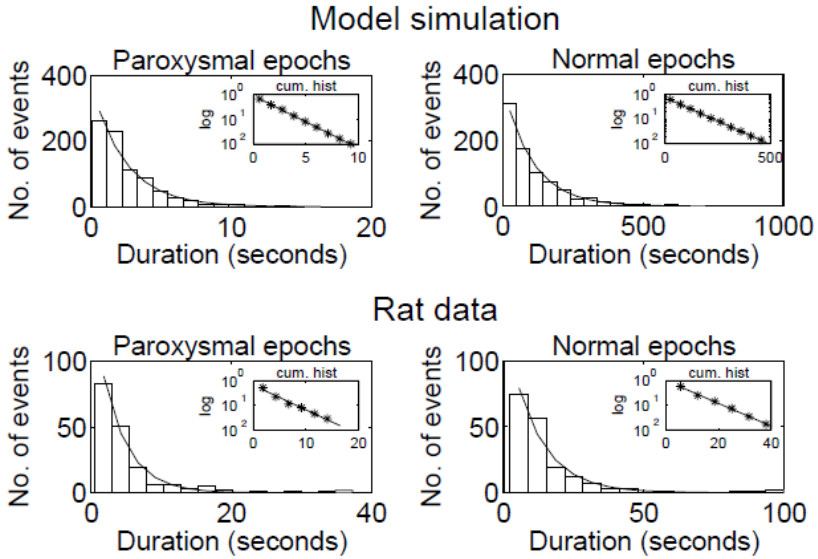
- each population simulated as a single lumped circuit
- this circuit can display many types of behavior: limit cycles, fixed points, bistable states

Bifurcation diagram and phase plane



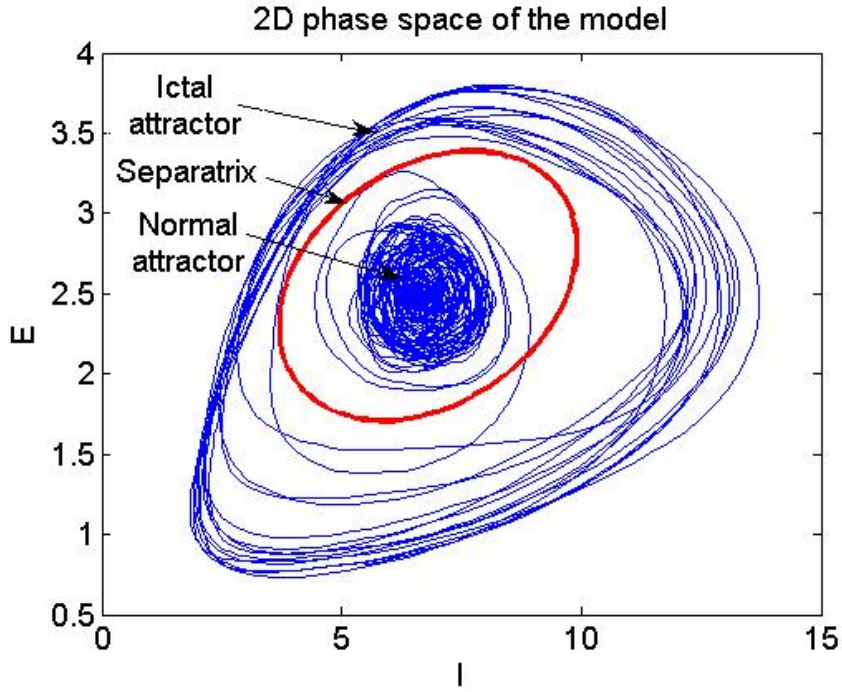
V_{Cx}= mean membrane potential of pyramidal cells
P_{Cx}= constant input to pyramidal cells
where should the brain's activity be in parameter space?

Phase planes



Random transitions between states support exponential distributions of lengths of paroxysmal discharges

$\Rightarrow$ brain should be in the bistable region



Simulated Results

randomly transitions from normal state to absence seizures due to bistability: stable fixed point coexists with larger stable limit cycle

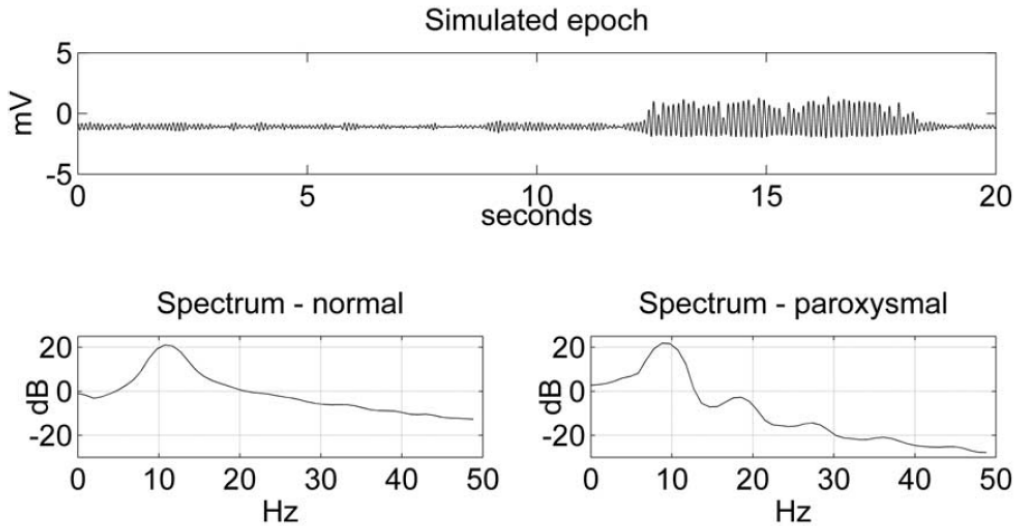
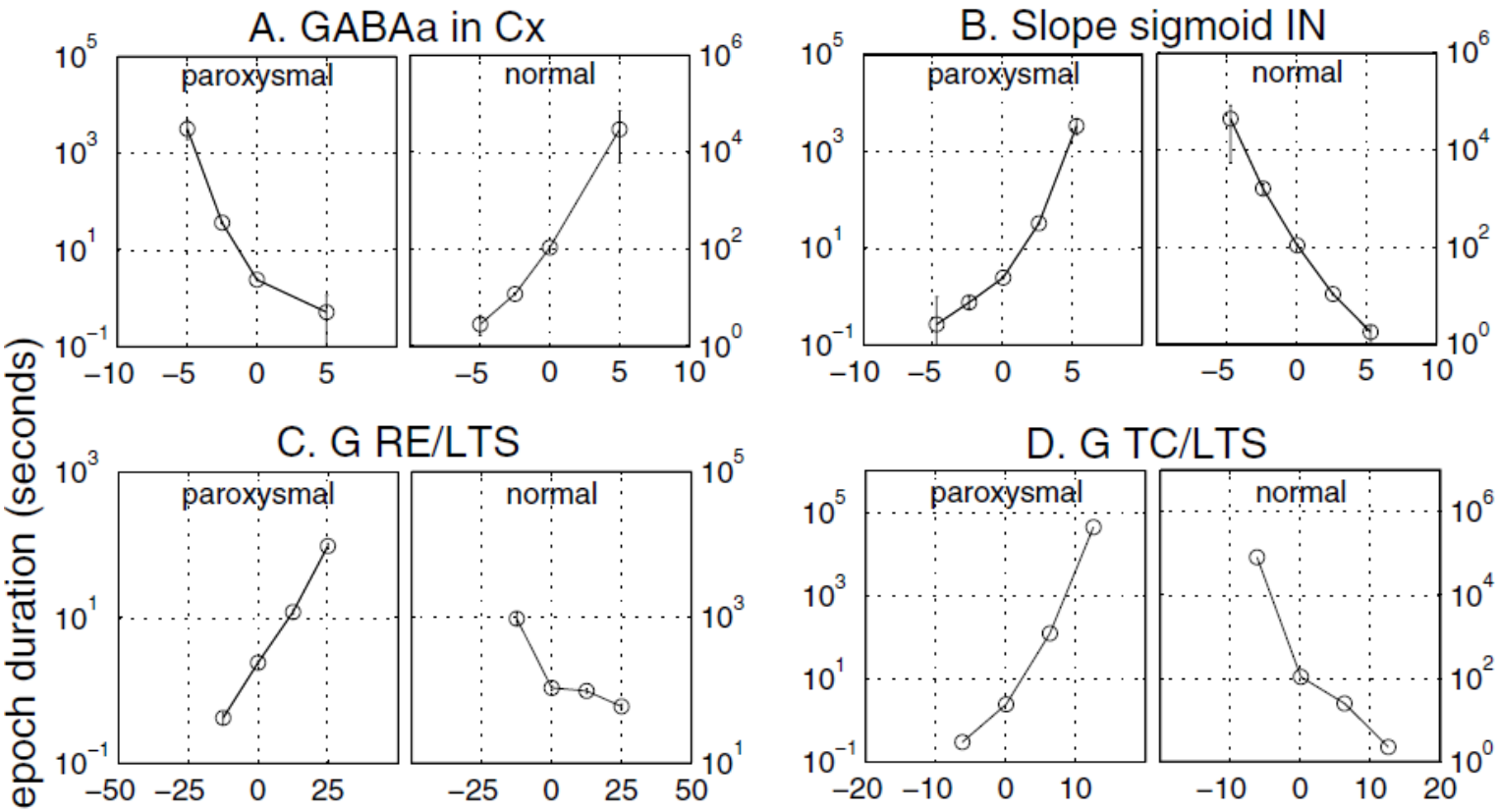


Fig. 2. Example of model output. Upper panel: 20 s of a simulation with the occurrence of a spontaneous paroxysmal episode. Lower panel: power spectra of simulated normal and paroxysmal activity. Dominant frequency of normal activity is around 11 Hz while that of paroxysmal activity is around 9 Hz.

Effect of Model Parameters

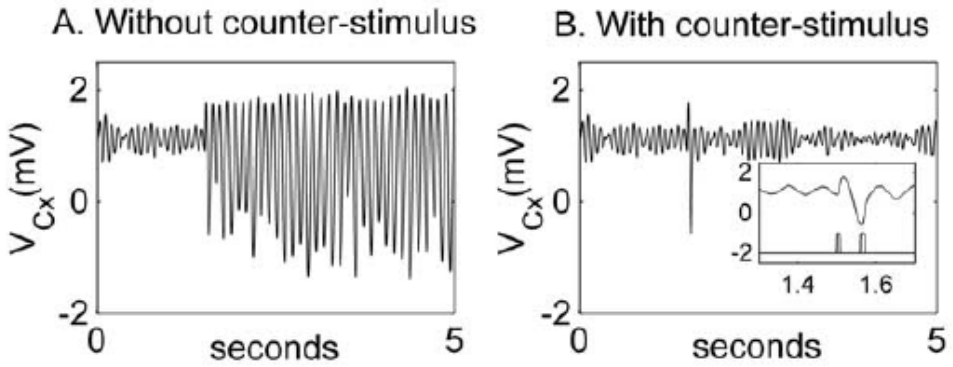
Realistic responses of the network to parameter changes:



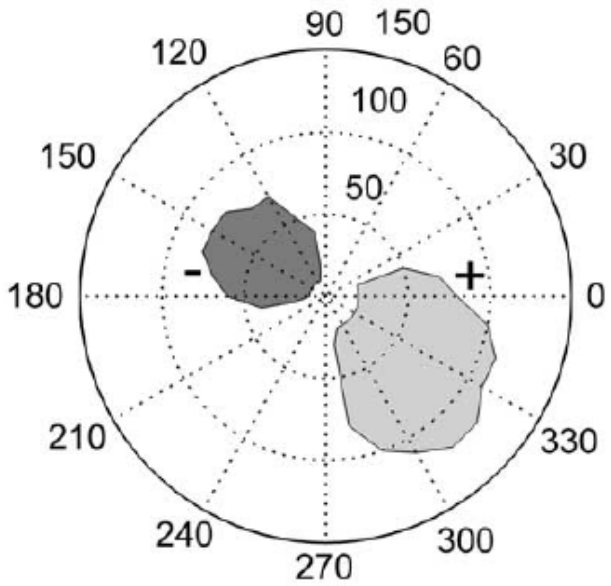
Simulated counter-stimulation

bistable region with limit cycle and steady state - should be able to push system back to steady state

– works only at a certain phase of the oscillation

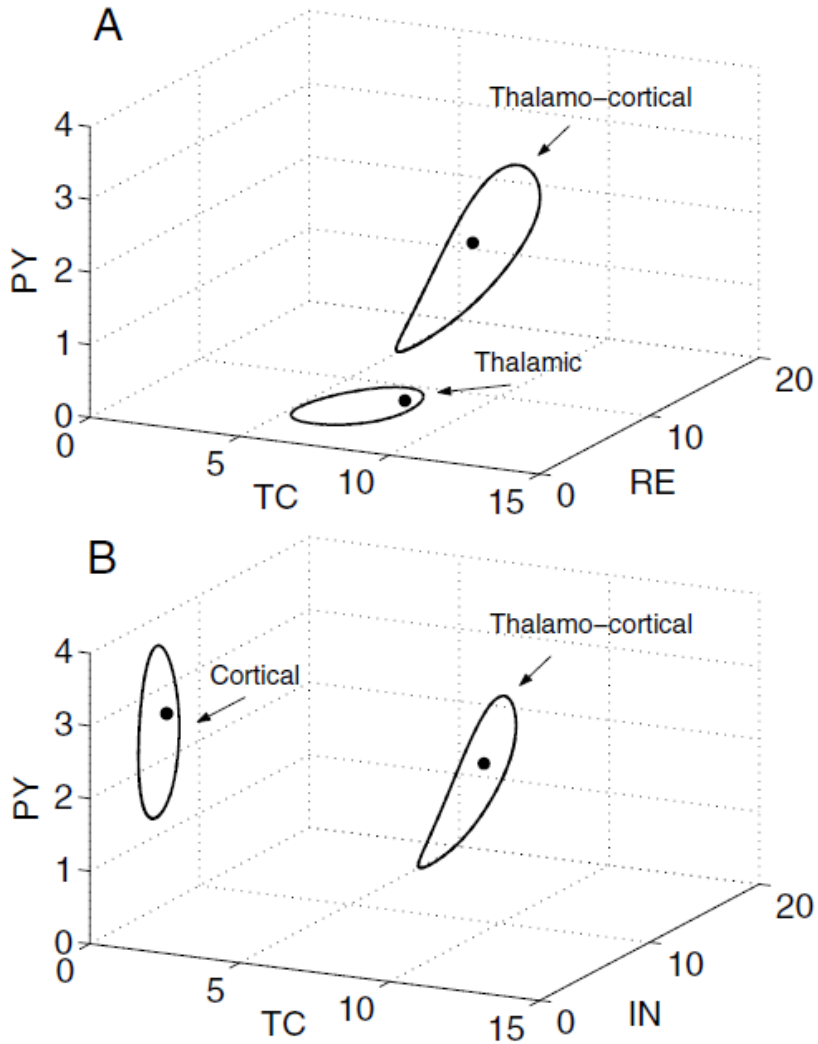


C. Counter-stimulus amplitude-phase plot



Single populations can exhibit bistability

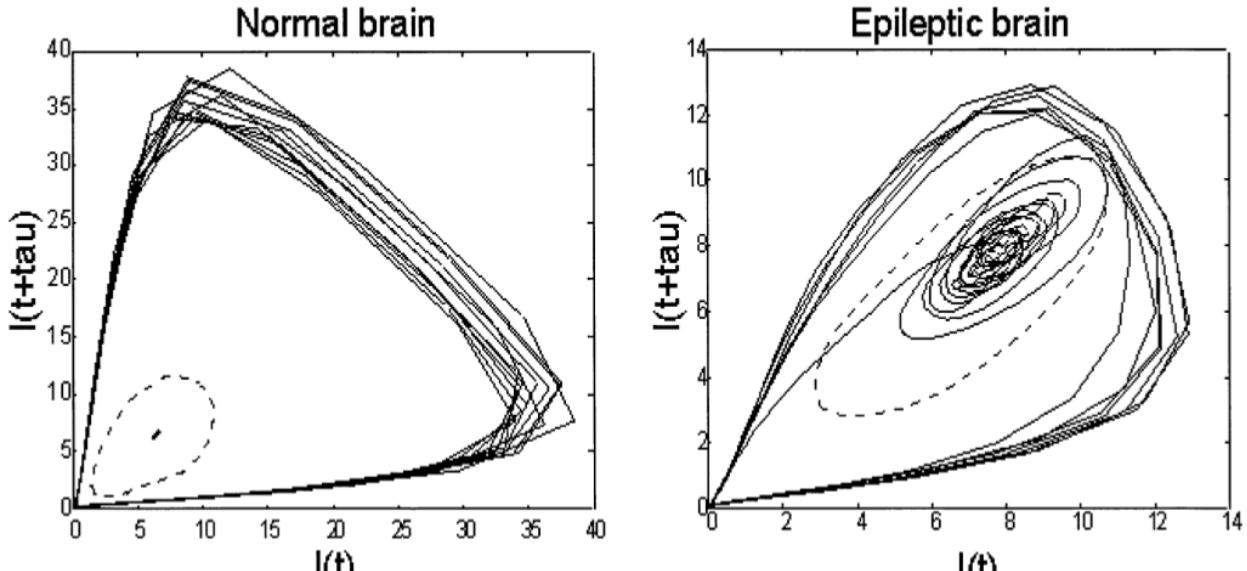
decreased inhibition or increased constant external input



GABA receptor antagonists affect seizure activity if applied to either cortex or thalamic neurons, thus they include two networks ...

Conclusions

- network is bistable and undergoes random transitions between normal activity and seizure-like oscillations
- probabilities of transitions depend on multiple model parameters
- seizure-like oscillations can be eliminated by a well-timed pulse
- absence-type seizures are unpredictable
  - other types of seizures may be based on this type of model AND be predictable - e.g. seizure onset causes changes in the location of the separatrix
- seizures caused by brain trauma may be due to increased cortical excitation not decreased cortical inhibition (homeostatic plasticity, Houweling et al, 2004)



Bistable Neuronal Network (full)