Epileptogenesis in Small World Neural Networks of the Hippocampus

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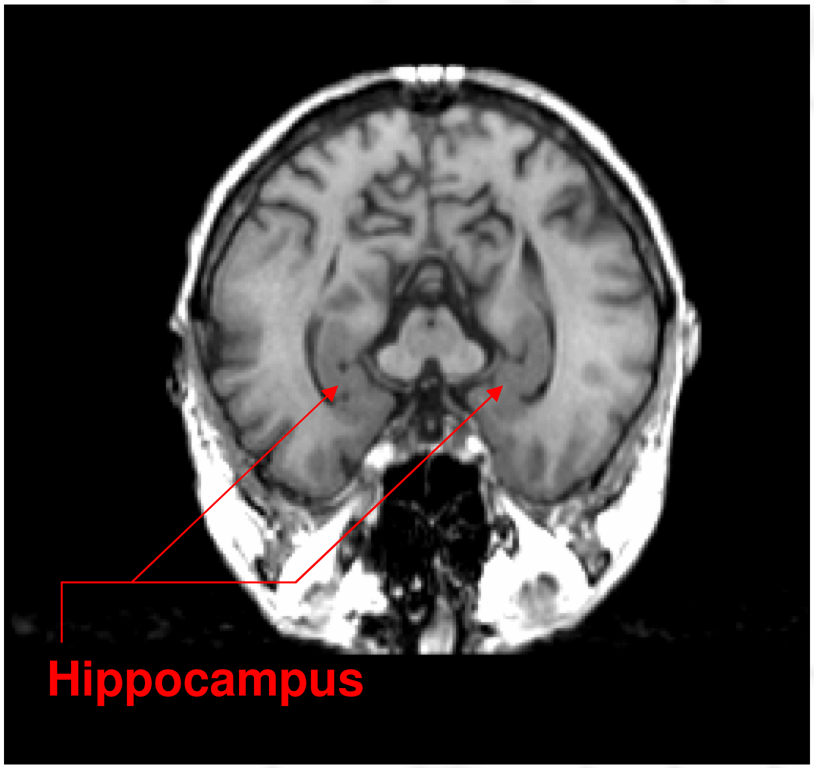
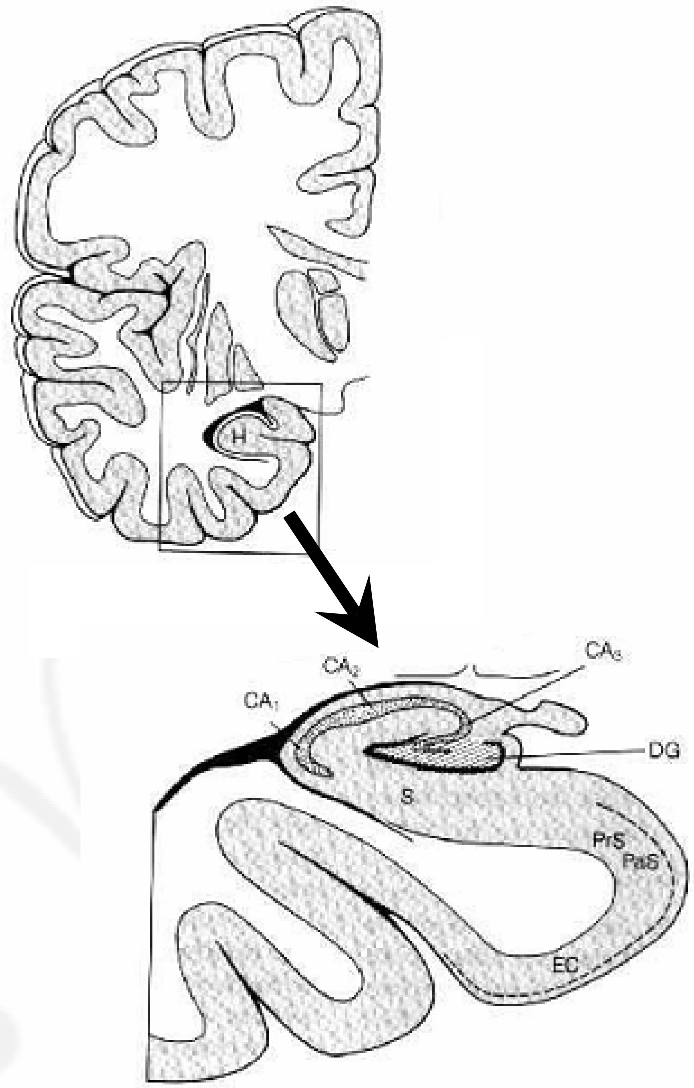
The Hippocampus

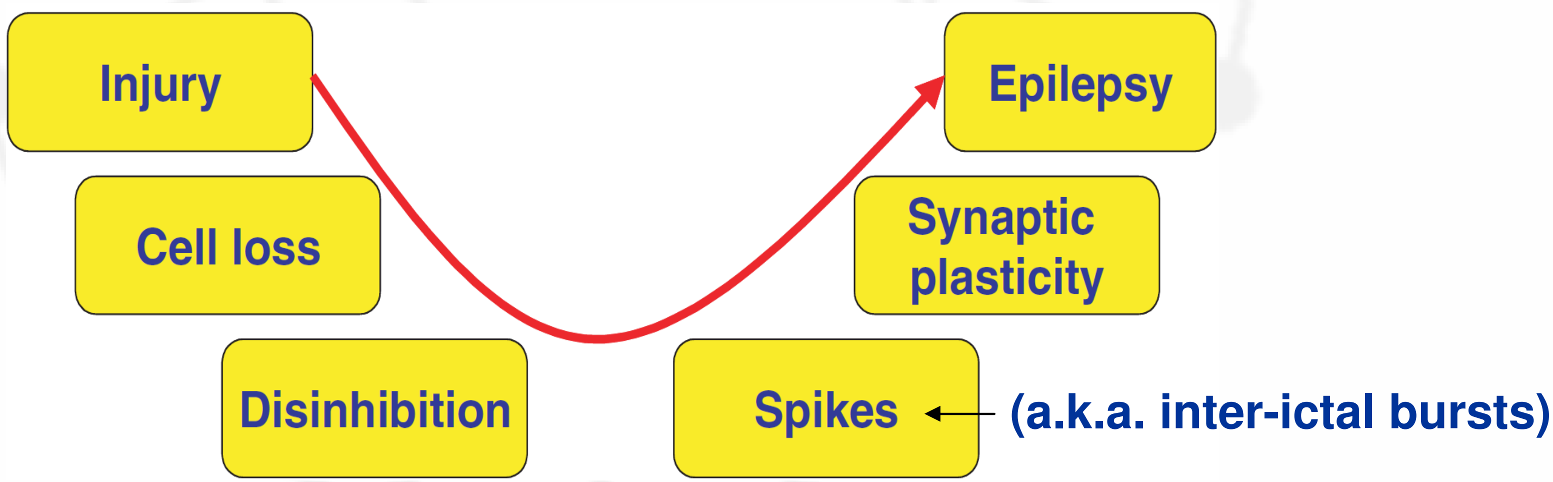




- Memory and learning
- Anatomically well-defined
- Temporal lobe epilepsy

Models of epileptogenesis

- Typically involve multiple steps …
- Long-term changes (esp. permanent)
- Short-term changes (esp. non-permanent)
- These involve connectivity changes



(Staley et al, 2005)

Primary objectives

- Epilepsy and network connectivity
  - What is the relationship?
  - Can it explain why epileptics have two types of epileptic activity?
    - Some networks “burst”
    - Others “seize”
- How does connectivity interact with other physiological parameters?

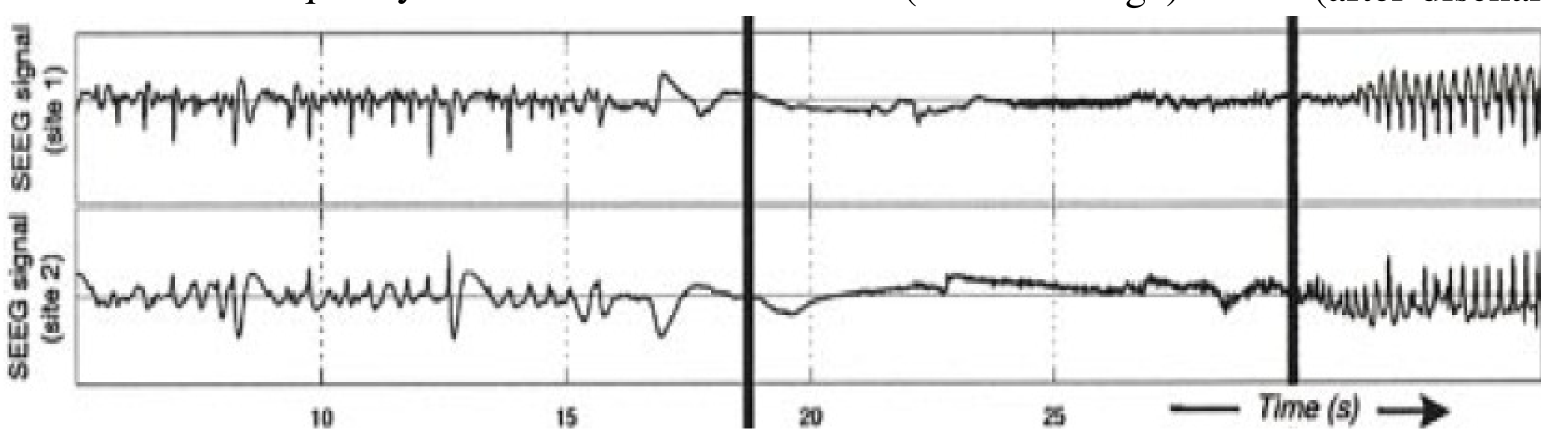
What are seizures?

- Seizure-like events > 1s
- Inter-ictal bursts ~ 0.1s
- Relationship poorly understood
- Population bursting vs. individual neural bursting
  (Shao et al., 2006)

Low-frequency bursts

SLE
(ictal discharge)

High-frequency bursts
(after-discharges)

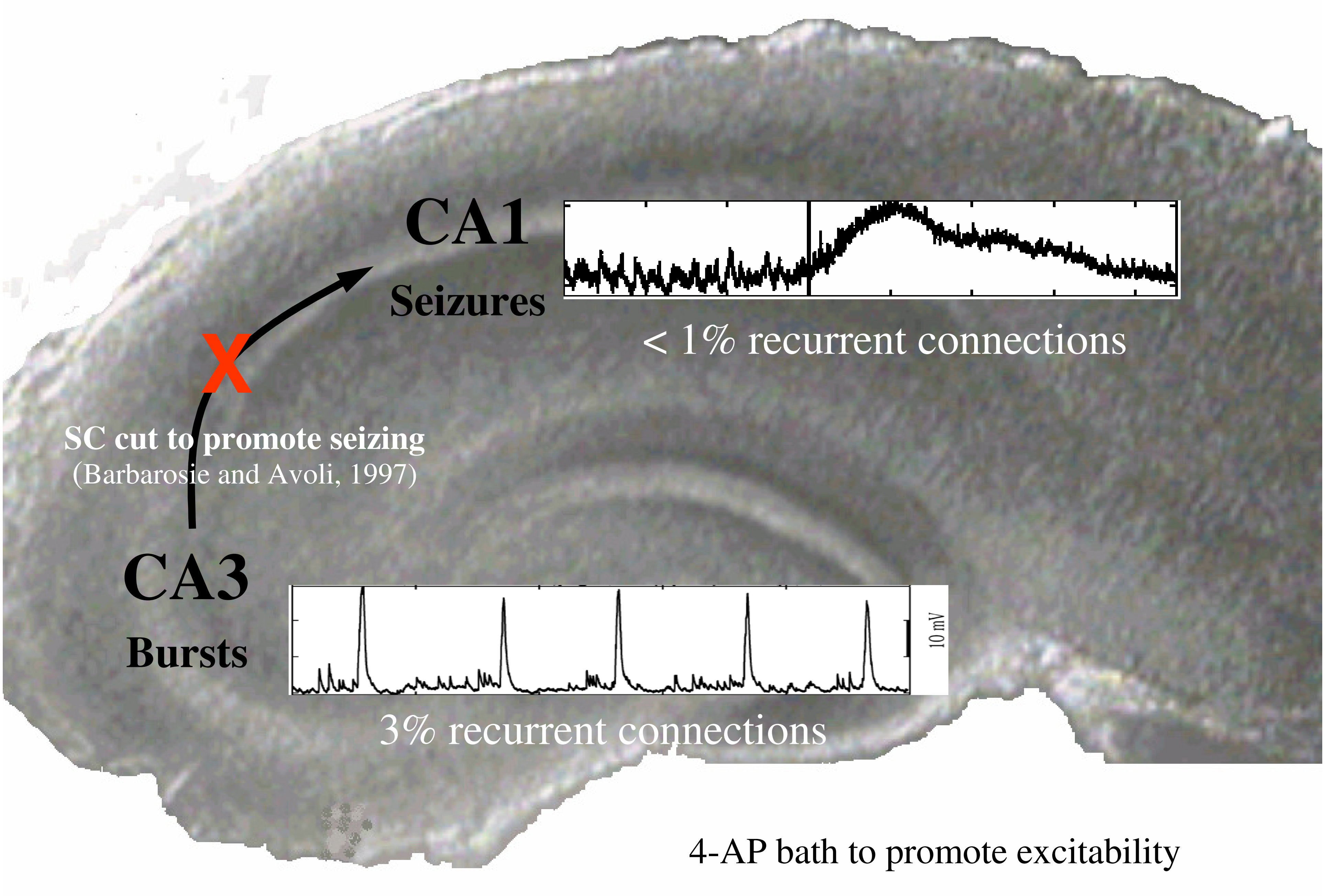


(Wendling et al, 2003)

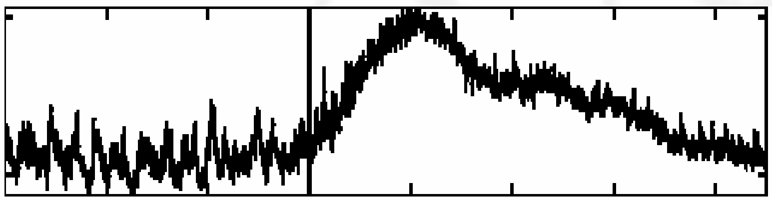
What are seizures?

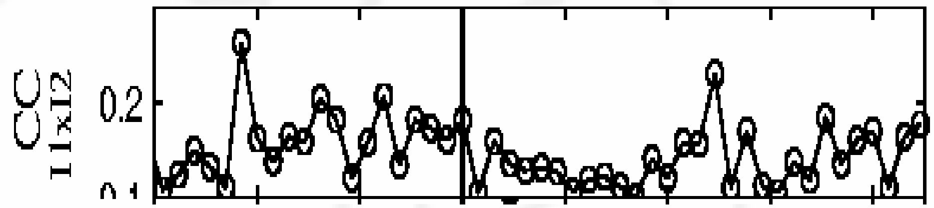
- Prevailing medical dogmas
  - Inter-ictal bursts are precursors to seizures ("damp kindling" hypothesis)
  - Seizure activity involves "hyper-synchronous" co-ordinated firing of many neurons
- Largely based on EEG observations

Rat hippocampus

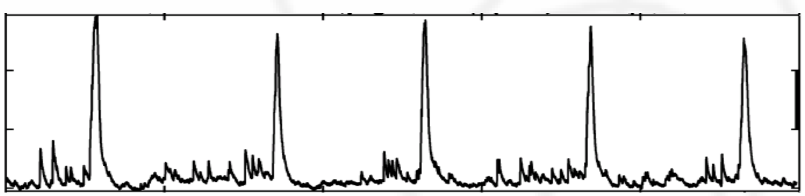


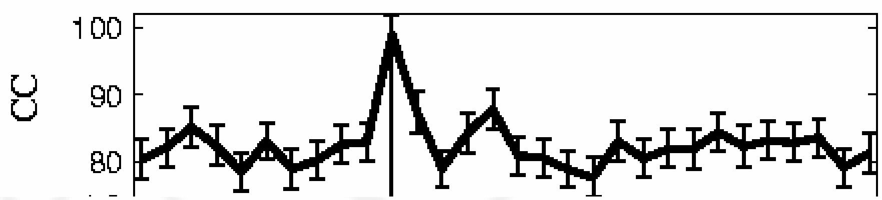
Neuronal activity has low correlation during seizure





Neuronal activity is highly correlated during bursts

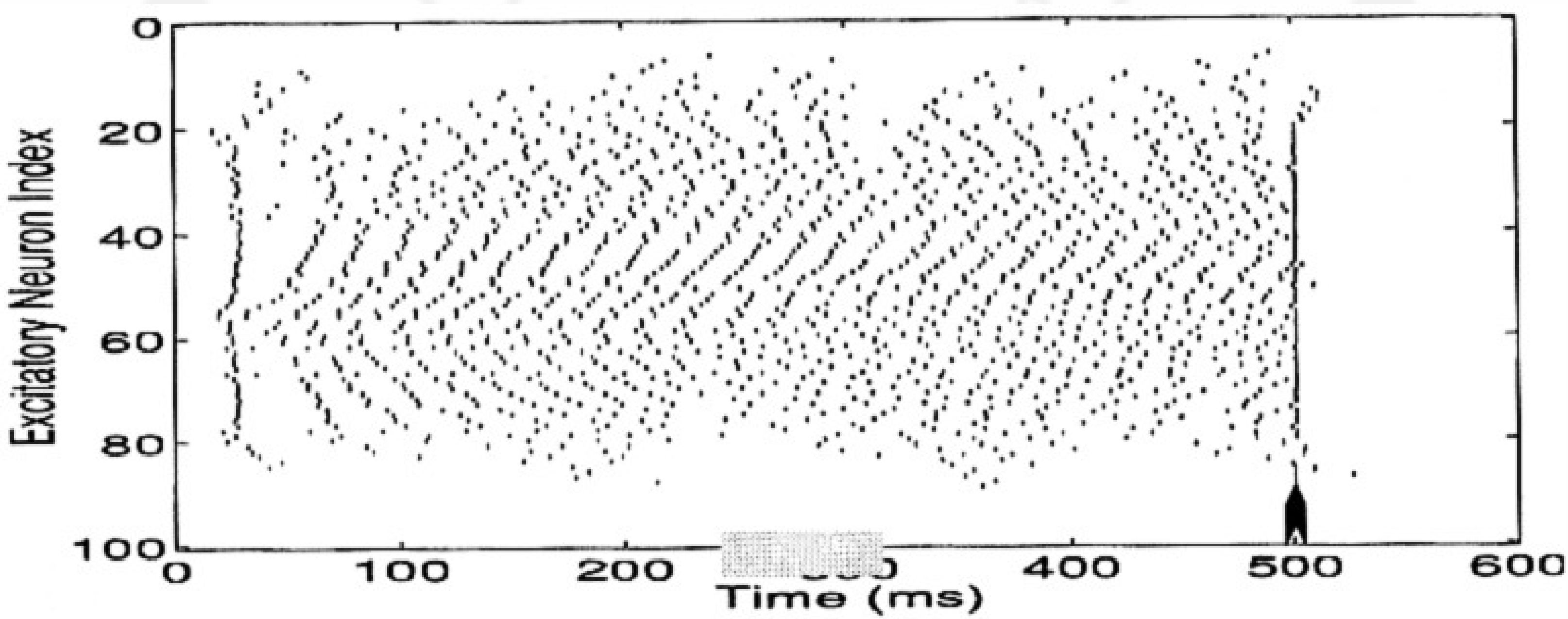




Netoff and Schiff, 2002 (Similar conclusions by Wendling et al, 2003; van Drongelen et al, 2003; Schindler et al, 2007)

De-correlation can be required for sustained network activity

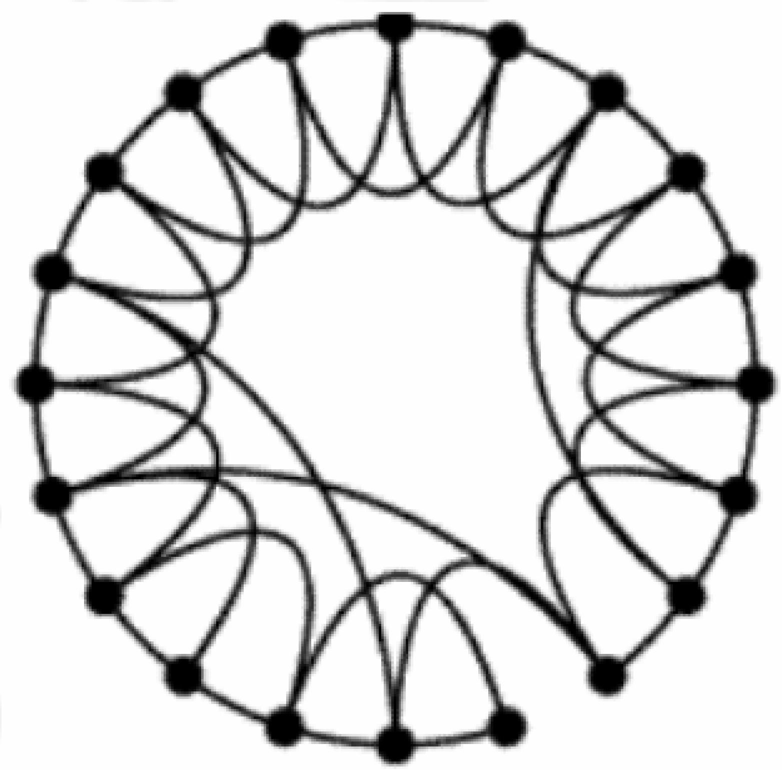
(Gutkin and Ermentrout, 1998)



Hypothesis: To sustain activity there needs to be a reserve of recruitable neurons

Model networks: small worlds

- Hippocampus
  - Neither a lattice nor randomly connected
  - Detailed anatomy emerging
- "Small world networks" can statistically mimic this
- Randomly rewired connections
  - Decrease average path length between two nodes
  - Maintain clustering
- Only three parameters needed

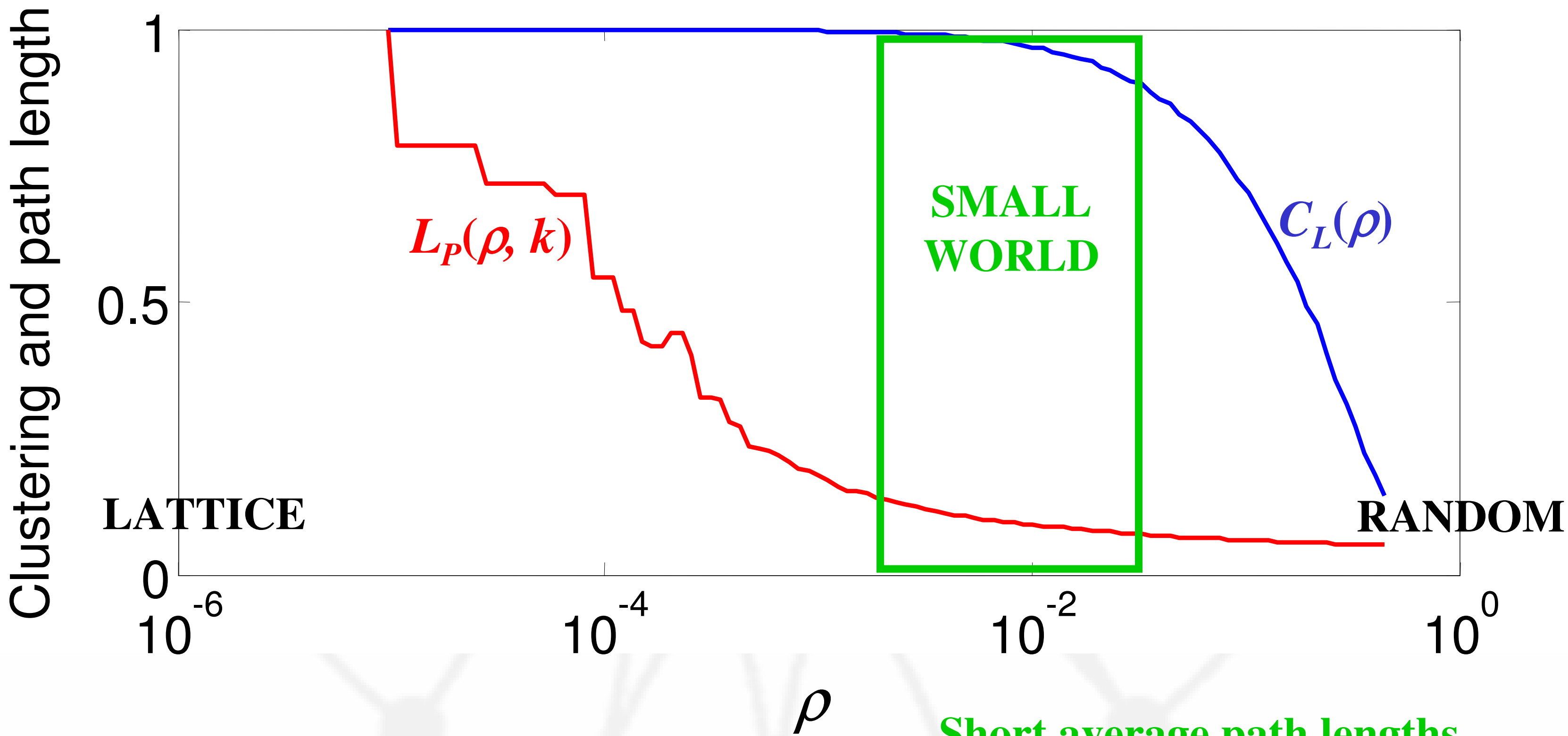


(Watts & Strogatz, 1998)

Connectivity parameters

- N
  - Number of nodes
- ρ
  - Probability a synapse is randomly rewired
  - “Proportion of long-distance connections”
- k
  - Proportion of N to which each neuron synapses
  - Also expressed as synapses/neuron

Small is a relative term

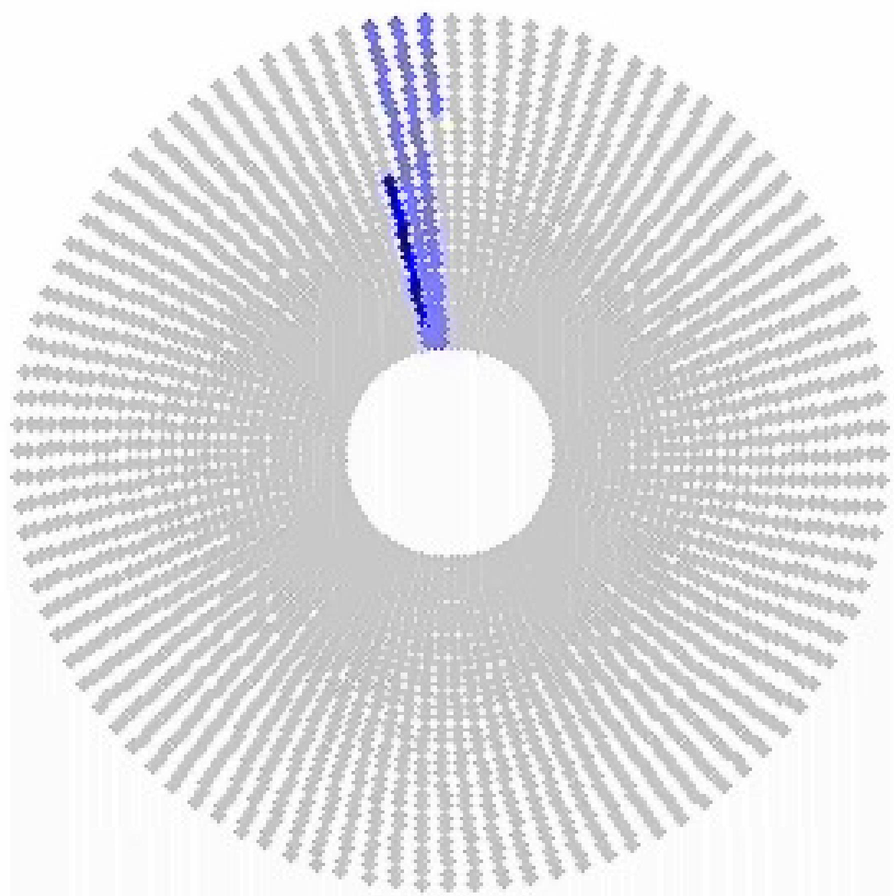


Short average path lengths

Network remains clustered

Stochastic network model

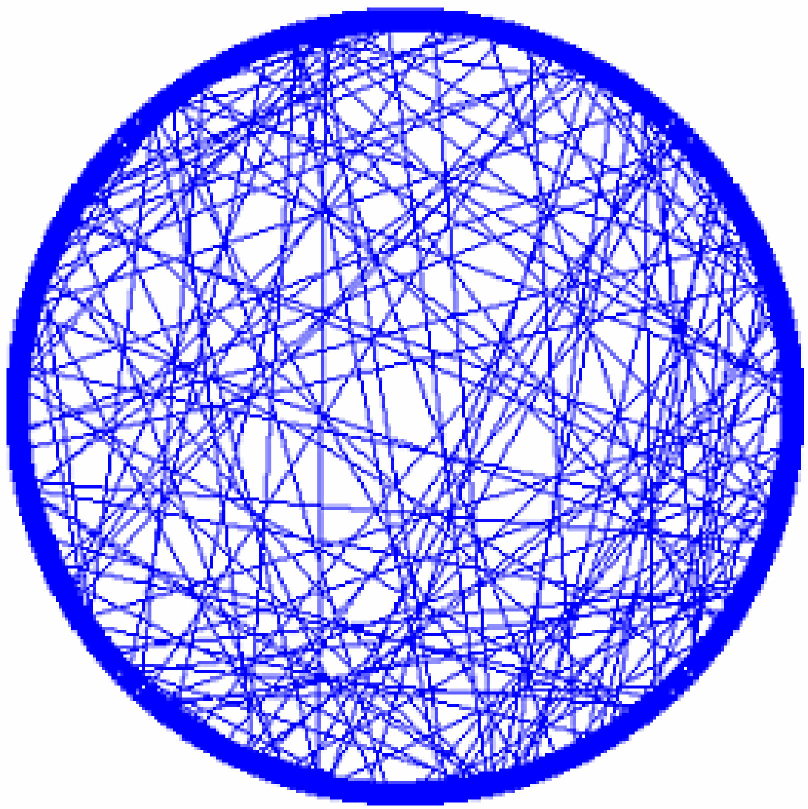
- Ring of excitatory neurons in SWN
  - Eliminates boundary conditions
  - Test broad ideas
  - Compare 3 neuron models
  - *Visual representation to see individual nodes*

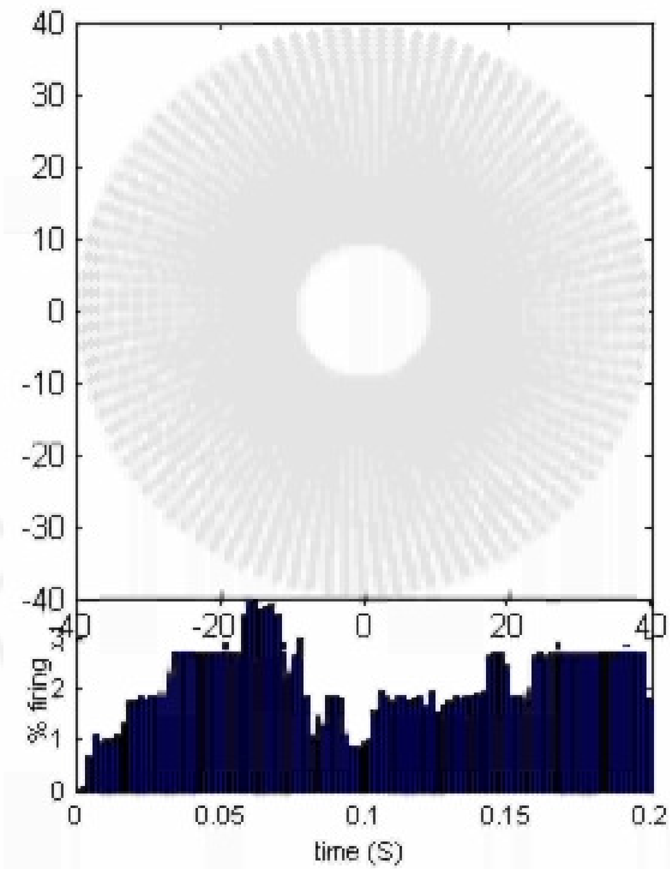


LIF network simulations: CA1

Seizing activity

N=3000, *k* = 30 synapses/neuron (1%), Proportion rewired ρ=0.005

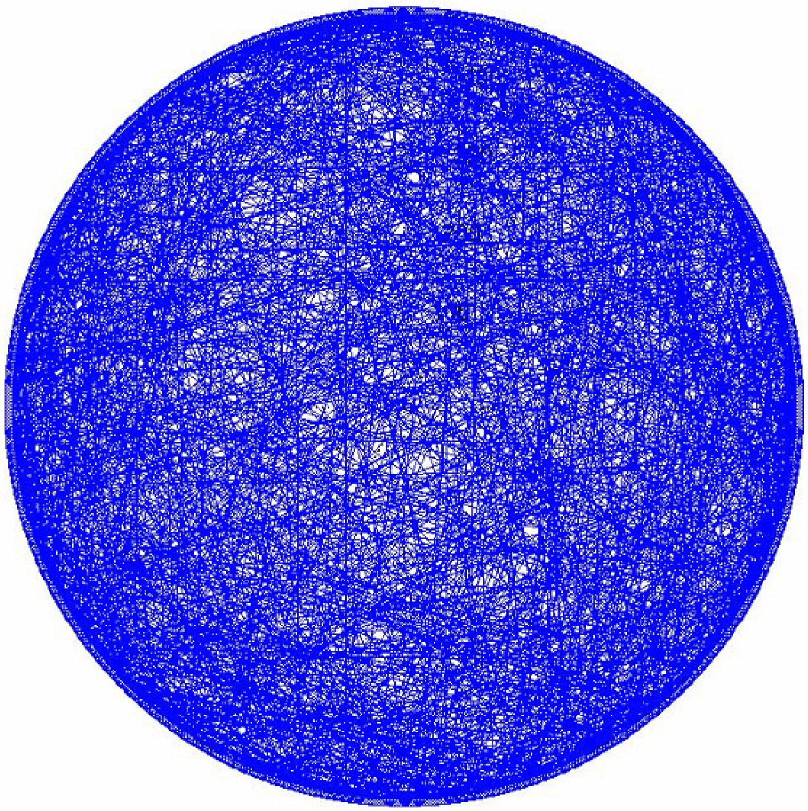


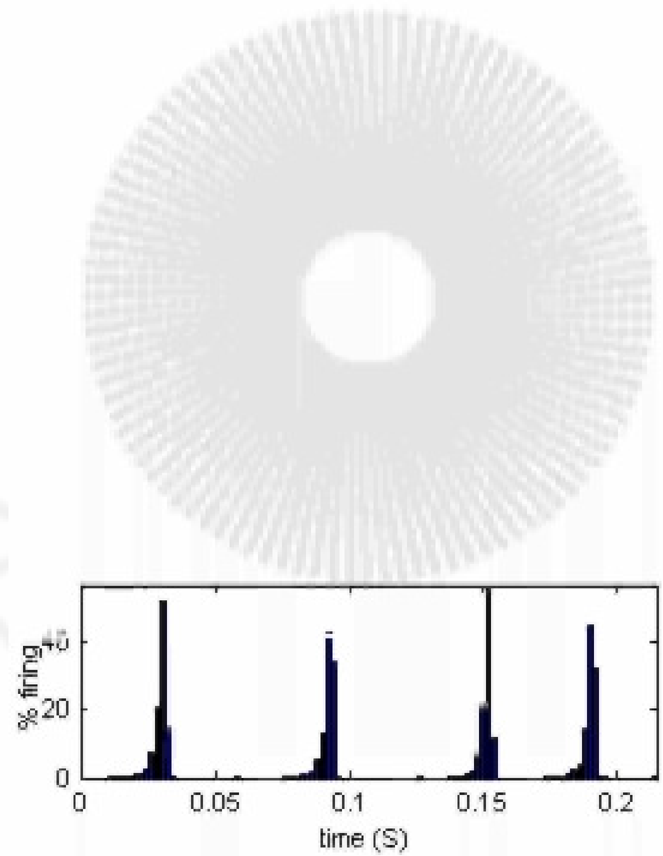


LIF network simulations: CA1

Bursting activity

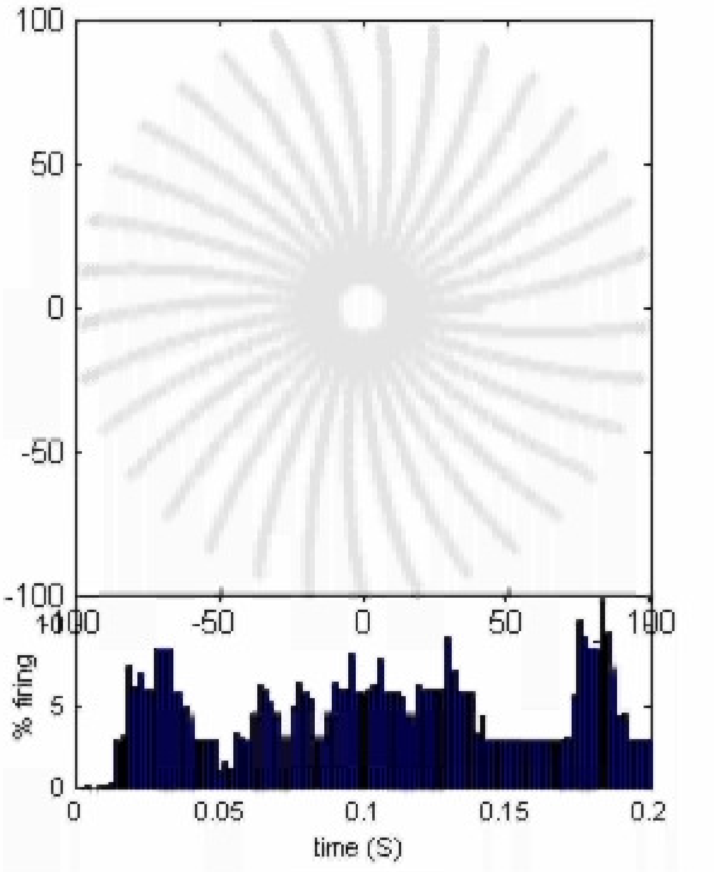
N=3000, *k* = 30 synapses/neuron (1%), Proportion rewired ρ=0.2





LIF network simulations: CA3

Proportion rewired $\rho = 0.0001$
Synapses/neuron $k = 90$



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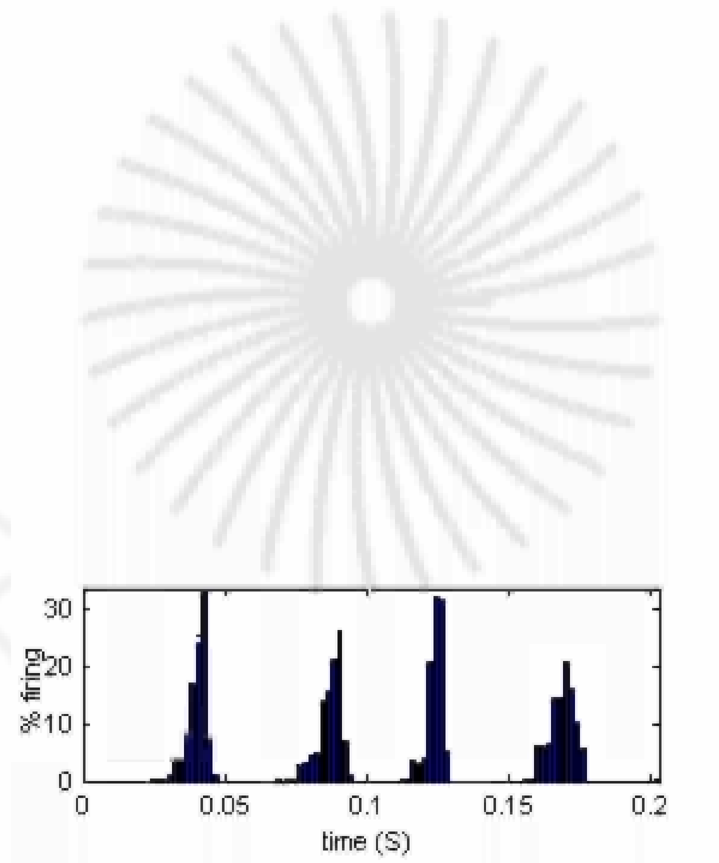
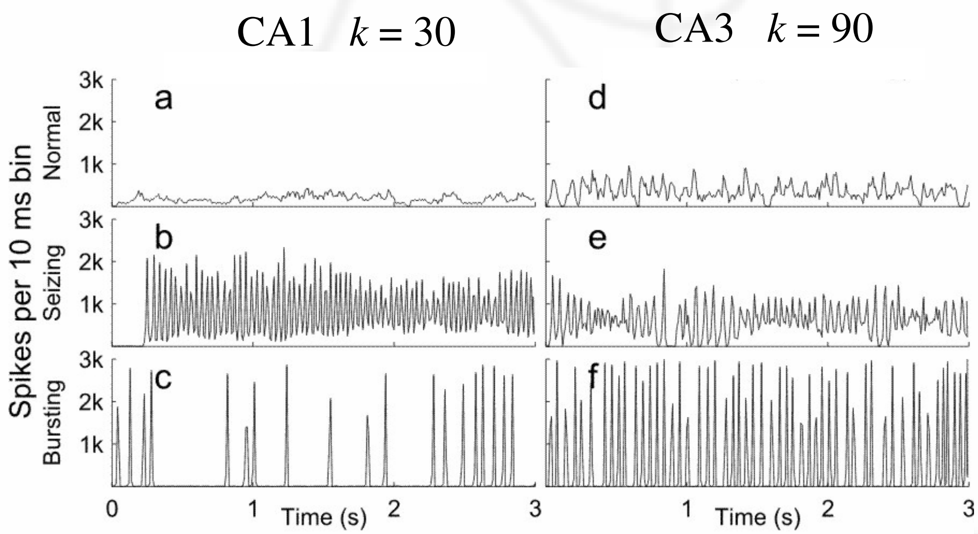
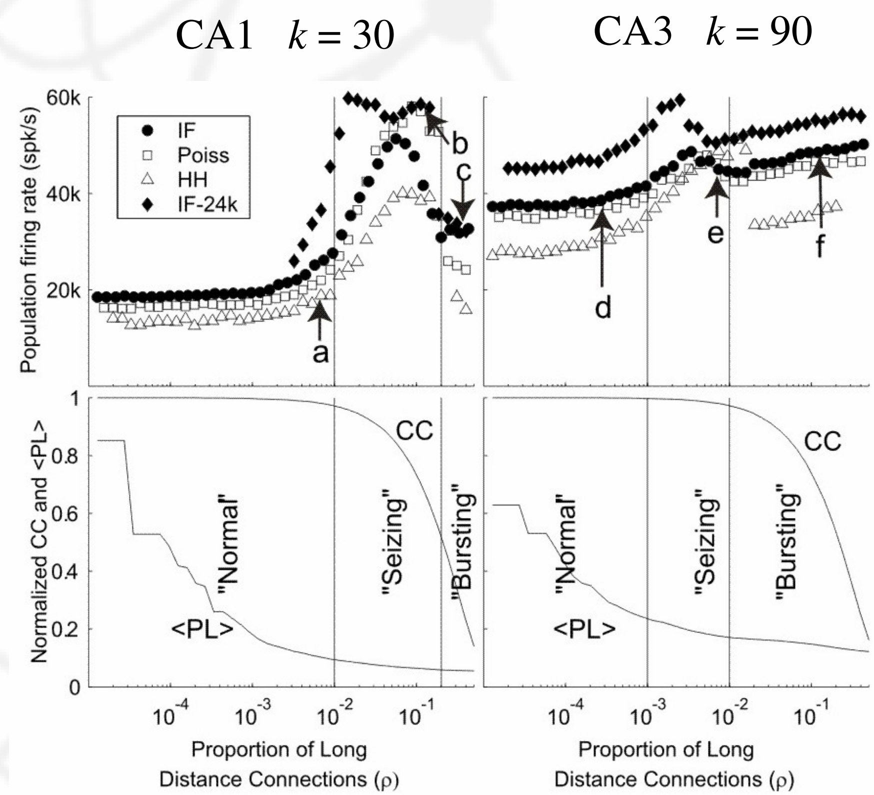


Network properties define transition from bursting to seizing





- Neuron models tested (parameters matched):
  - Leaky integrate-and-fire
  - Poisson spike train
  - Stochastic Hodgkin-Huxley

Param's for Poisson neuron model

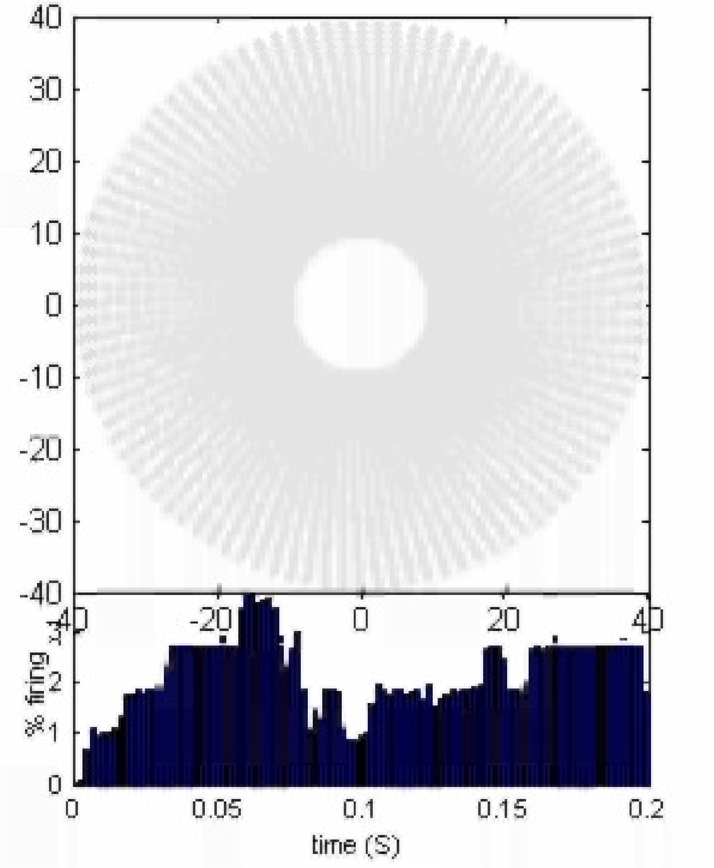
N - **number of neurons** in the network (3000)
k - **number of synapses/neuron** (all synapses start with coupling only to immediate neighbors)
ρ - **probability** that a synapse is broken and **rewired** to random location in the network

p_1 **-** **synaptic efficacy** (0.025):
P(neuron fires | one synaptic spike input)
e.g. $\propto$ ratio of excitation to inhibition
p_2 **-** P(two or more local neurons fire | one neighbour fires)
(using Binomial theorem)

$$p_2 = 1 - (1 - p_1)^k - (k-1)\, p_1 (1 - p_1)^{k-1}$$

S **-** **spontaneous neuron firing rate**
R **-** **refractory period** (multiple of delay time)

How does activity propagate through the network?



- Discrete-time dynamical systems analysis of **average number of waves** in network at any given time
- Qualitative description of the stochastic simulated models
- "Forest fire" model (Bak et al, 1990)

New # of waves = current # of waves

+ new waves

– dying waves

Difference equation for waves

- Essentially a discretized "master equation"
- Include recent history of activity in dynamics?

No $\rightarrow$ 1-dimensional map $\boxed{w_{i+1} = w_i + n_i - d_i \equiv f(w_i)}$

Yes $\rightarrow$ (1+R)-dim map

$$\boxed{\begin{aligned} w_{i+1} &= w_i + n_i - d_i \\ &\equiv f(w_i, w_{i-1}, \ldots, w_{i-R}) \end{aligned}}$$

w_i = number of wave fronts
n_i = number of new wave fronts
d_i = number of dying wave fronts due to collision/annihilation

Assumptions of the maps

- Two post-synaptic neurons fire within a local neighbourhood (k neurons) $\Rightarrow$ all k will fire at time i+1
  - Creates two wave fronts on ring
  - Reasonable because of the large overlap of local connections

- Travelling wave front contains exactly $\alpha = k/2 - 1$ neurons

- Refractory tail has size αR in 1D map
  - Or sum activity over previous R steps in (1+R)-dim map

- Maps valid only at low activity levels
  - Derivation of n_i and d_i require assumption that network activity was far from saturation

The one-dimensional map

$$w_{i+1} = w_i + n_i - d_i \equiv f(w_i)$$

$$n_i = \theta w_i e_i + s_i$$

$$d_i = 2 w_i \alpha / e_i$$

$$e_i = N - w_i \alpha (1+R)$$

$$s_i = 2 S p_2 e_i$$

$$\theta = \frac{2\alpha\rho k p_1 p_2}{N}$$

This parameter contains all the network properties that are fixed

w_i = number of wave fronts

n_i = number of new wave fronts

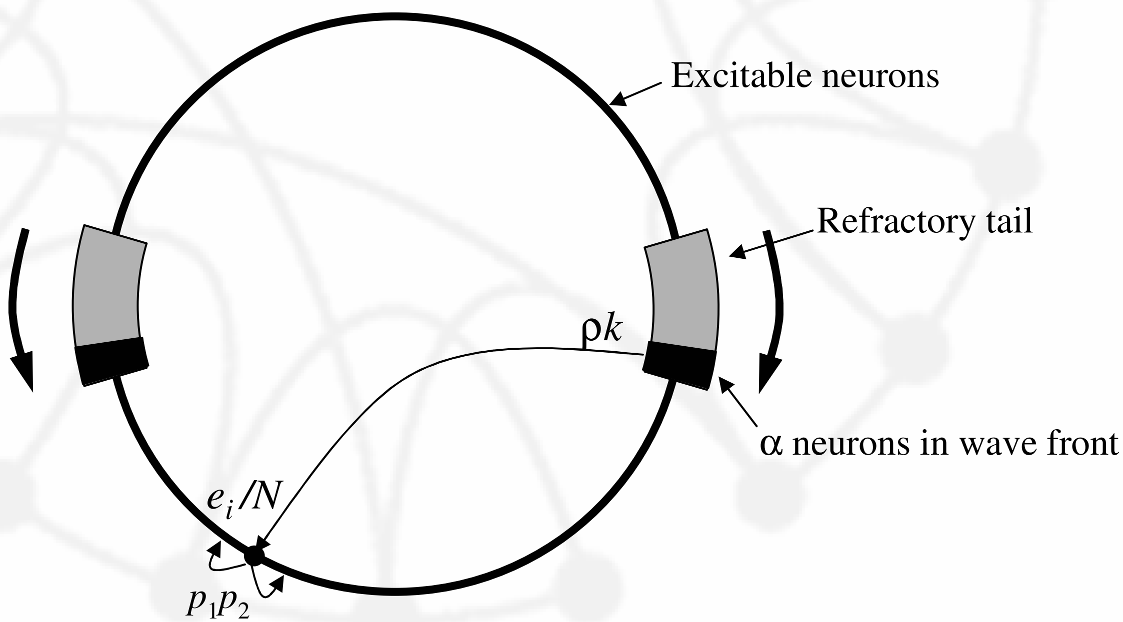
d_i = number of dying wave fronts due to collision/annihilation

e_i = number of excitable neurons

s_i = number of spontaneous waves (<< those due to coupling)

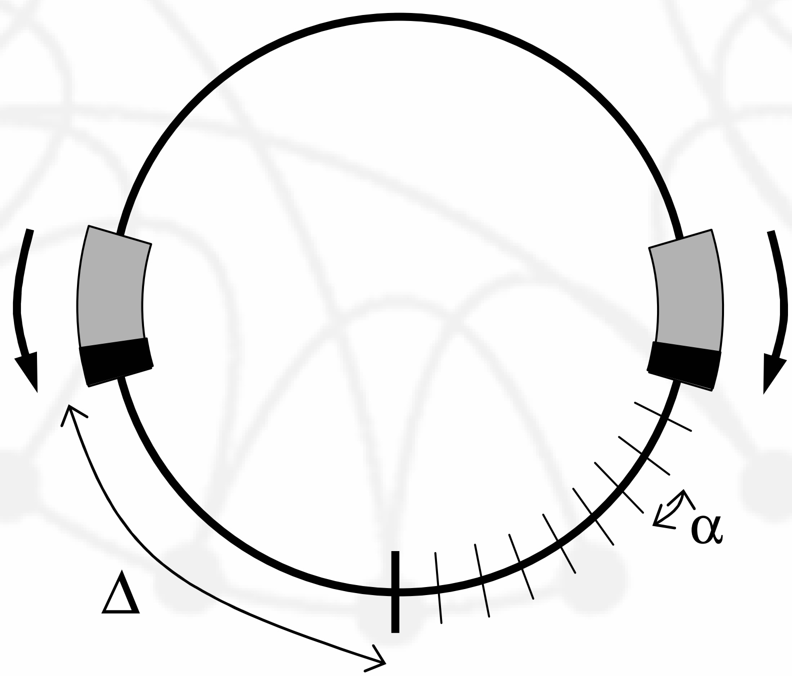
Derivations: new waves

- Each wave front = α neurons, each having k connections
- On average, ρk of these are long-distance, of which only the proportion e_i/N arrive at excitable cells
- Activity along these connections spark 2 wave fronts with probability $p_1 p_2$ (condensing two time-steps worth of synaptic transmission into one)



Derivations: dying waves

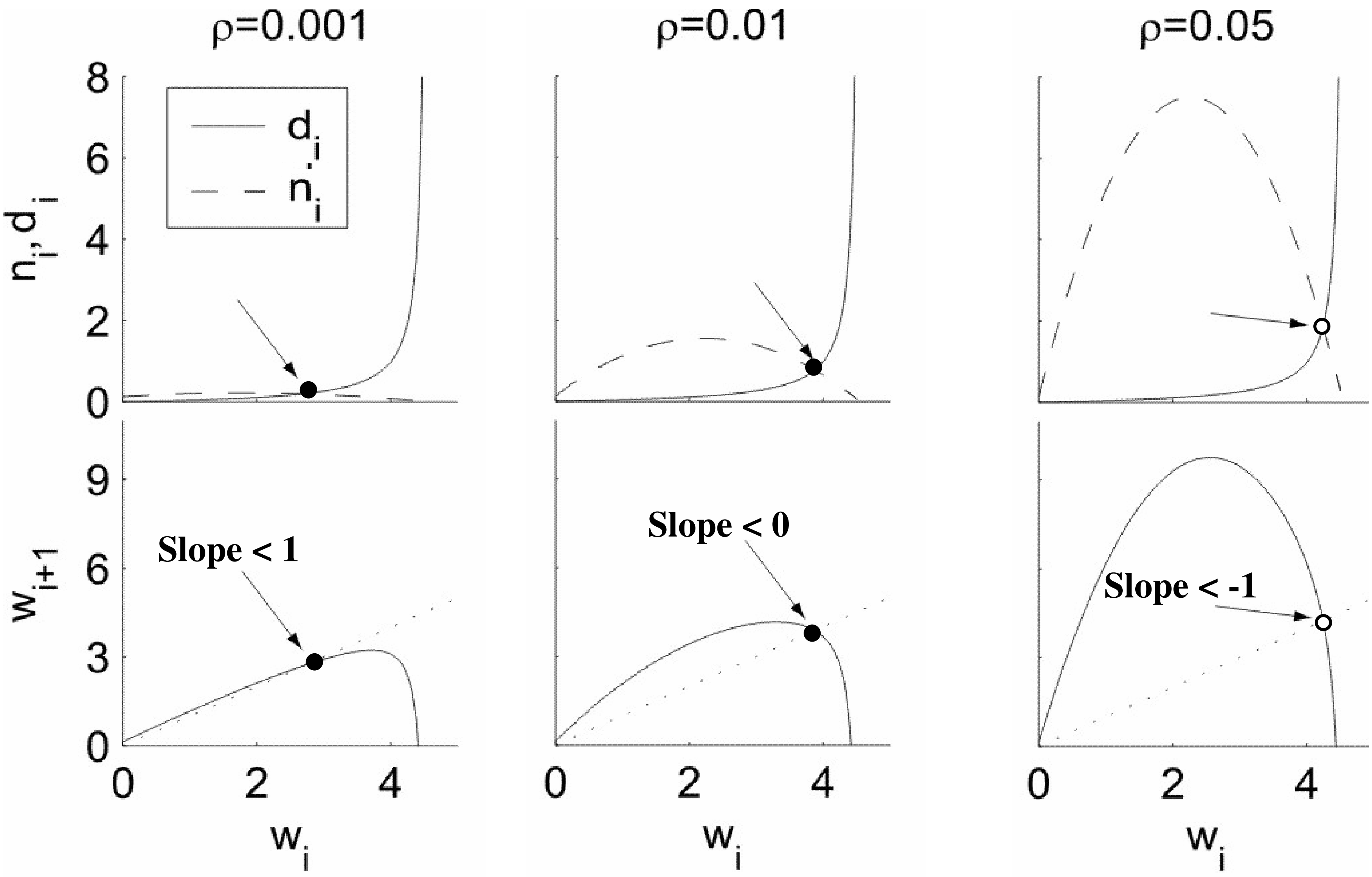
- Assume all waves evenly spaced on average
- # of gaps (containing excitable cells) = # waves
- Each wave travels Δ = ½ the excitable neurons per gap before annihilation, i.e. $\Delta = e_i / (2w_i)$
- … traversed in Δ/α time steps
- Thereby killing waves at a rate of $e_i / (2w_i\alpha)$ per step



Explore parameter roles

- How do parameters affect network behaviour?
  - e.g. corroborate and predict simulation outcomes
- Qualitative analysis of discrete dynamics
  - Equilibria ~ expected number of waves
    ($f(w^*) = w^*$ for fixed points)
  - Stability ~ sustainability of network activity
    ($|\lambda| \equiv |f(w^*)| < 1$ for attracting)
  - Strength of stability ~ variance (indicates fluctuations)
- Exemplify by varying ρ and p_1 for 1D map

Stability analysis at equilibrium



Stability analysis at equilibrium

Slope < -1

↕

Flip bifurcation
(unstable f.p.)

↕

High amplitude
oscillations

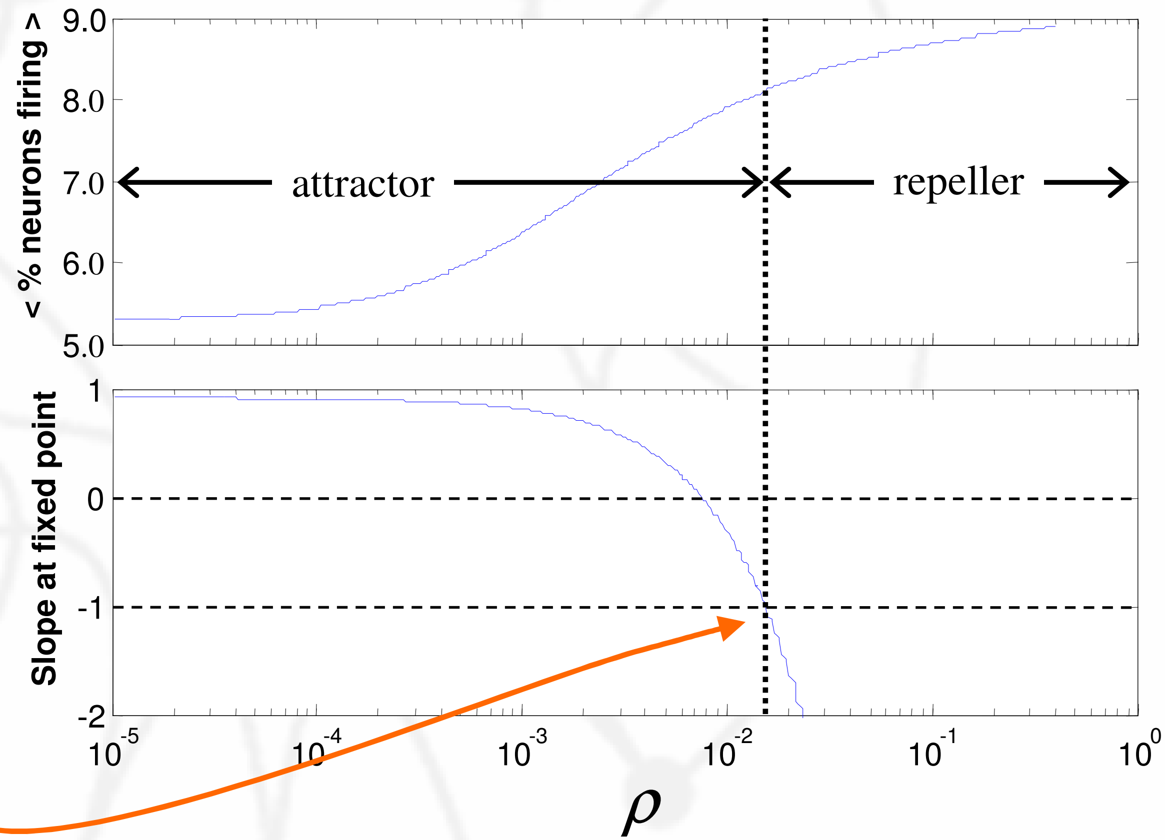
↕

Activity saturates
(unsustainable)

↕

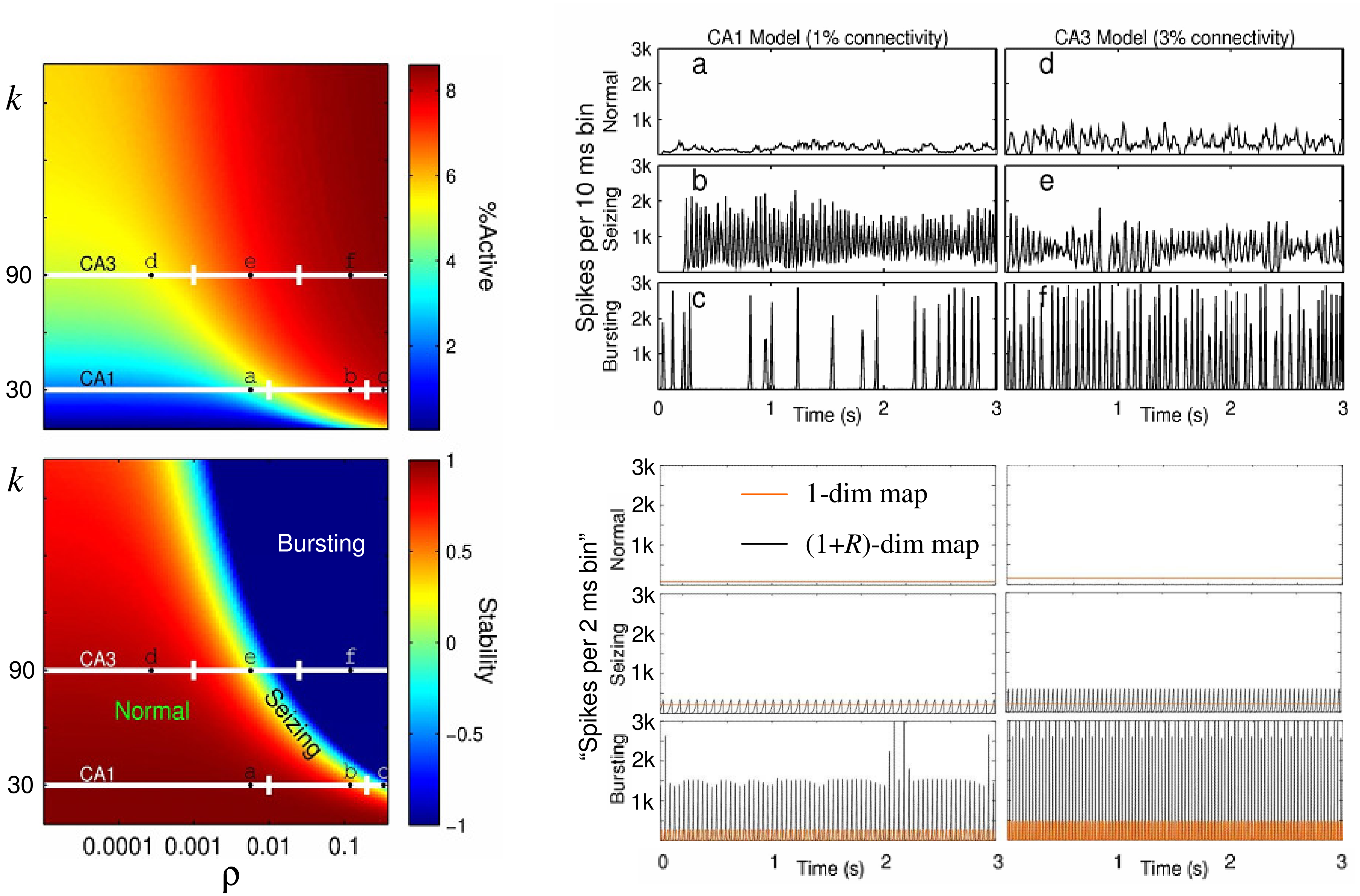
Burst

Fixed point position and slope as function of
% long distance connections in network



$N = 3000, \quad k = 90$

Maps capture the trends



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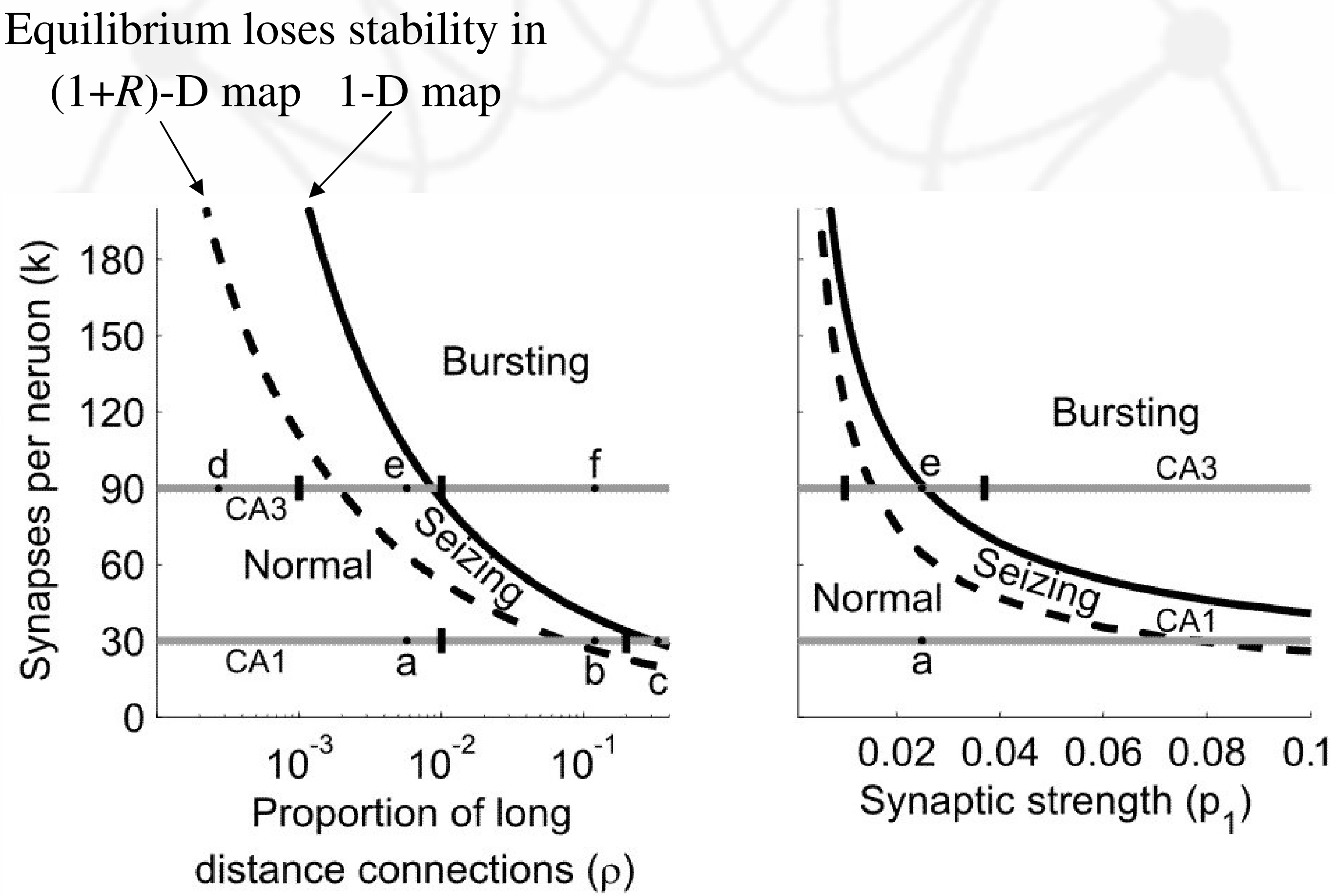


Predicts increasing synaptic efficacy causes network to burst in CA3 before CA1

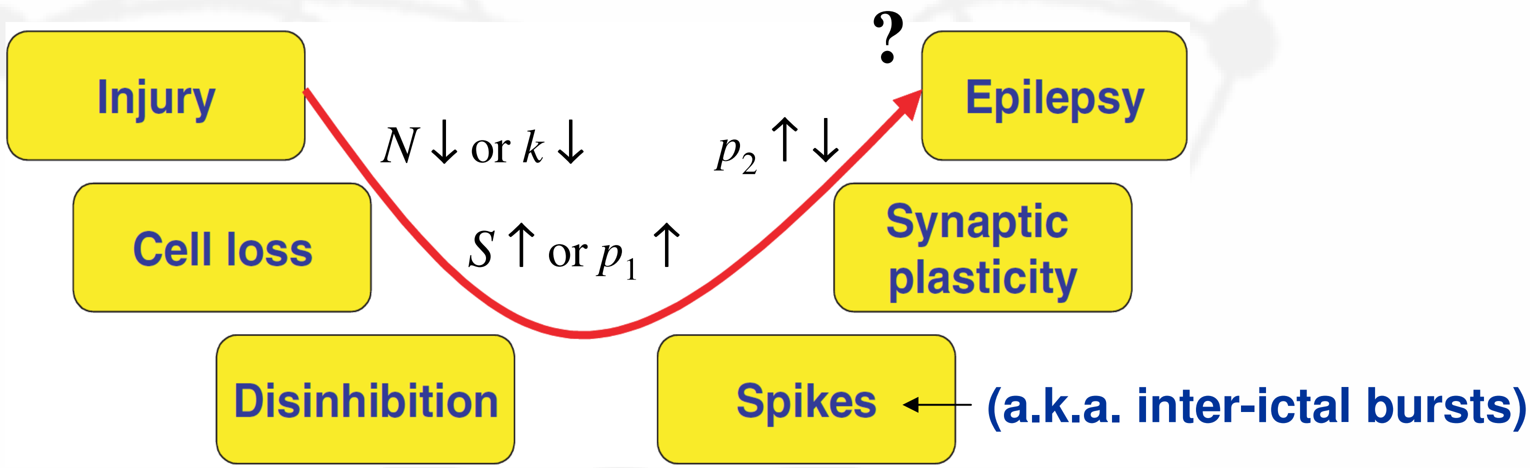
Summary of results

- Suggests broad relationship between network connectivity and temporal lobe epilepsy
  - Denser networks burst
  - Sparser networks seize
- Bursts are more synchronous than seizures
- Bursts may not be "pre-seizures"
  - Network-based mechanism
  - Not "damp kindling" in this case

Physiological implications

- Simple map representation of network dynamics
  - Predicts roles for physiological parameters (alone or in combo)
  - Encodes basic assumptions
  - Validated against our simulations
  - Predictions easier to generate/analyze than using large data-driven simulations

- **Basis for predicting result of parameter changes in mechanistic, computational models**



Physiological implications

- DG shows SWN connectivity (Dyhrfjeld-Johnsen et al., 2006)
  - Specific sclerosis of distantly-projecting hilar neurons
  - Sprouting of mossy fibres
- Neocortex may behave differently
  - Different connectivity
  - Intrinsic bursting neurons (NaP) (van Drongelen et al., 2005)
- Could try this methodology in
  - Developmental networks
  - Migraine models
- Recent work has studied statistics of waves in SWNs and scale-free networks (some in 2D)

  (Roxin et al., 2004; Ursino & La Cara, 2006; Beggs & Plenz, 2004; Singer et al., 2006; Carvunis et al., 2006; French & Gruentstein, 2006)

Inhibition and excitation

- Hippocampus ~ 80% excitatory, 20% inhibitory
- Inhibition important to study drug effects
  - Slower inhibition may switch off SLEs
- Inhibition + excitation ~ lower excitation?
  - Inhibitory cell connectivity uncertain
  - Synchronous w/ excitation? (P. Velazquez & Carlen, 1999)
- Mark Kramer (B.U.) working on models