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)

(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

CA3

Bursts

< 1% recurrent connections

SC cut to promote seizing
(Barbarosie and Avoli, 1997)

CA1

Seizures

3% recurrent connections

4-AP bath to promote excitability
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

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

(Gutkin and Ermentrout, 1998)
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

- $\rho$
  - 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

Clustering and path length

$C_L(\rho)$

$L_p(\rho, k)$

SMALL WORLD

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 $\rho=0.005$
LIF network simulations: CA1

Bursting activity

$N=3000, k = 30 \text{ synapses/neuron (1%)}, \text{ Proportion rewired } \rho=0.2$
LIF network simulations: CA3

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

Proportion rewired $\rho = 0.01$
Synapses/neuron $k = 90$
Network properties define transition from bursting to seizing

CA1 \( k = 30 \) \hspace{1cm} CA3 \( k = 90 \)

- 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)

\( \rho \) - **probability** that a synapse is broken and **rewired** to random location in the network

\( p_1 \) - **synaptic efficacy** (0.025):

\[ P(\text{neuron fires | one synaptic spike input}) \propto \text{ratio of excitation to inhibition} \]

\( p_2 \) - \( P(\text{two or more local neurons fire | one neighbour fires}) \)

(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  →  1-dimensional map \[ w_{i+1} = w_i + n_i - d_i \equiv f(w_i) \]

Yes  →  (1+R)-dim map \[ w_{i+1} = w_i + n_i - d_i \equiv f(w_i, w_{i-1}, \ldots, w_{i-R}) \]

\( w_i = \text{number of wave fronts} \)
\( n_i = \text{number of new wave fronts} \)
\( d_i = \text{number of dying wave fronts due to collision/annihilation} \)
Assumptions of the maps

• Two post-synaptic neurons fire within a local neighbourhood (k neurons) ⇒ 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 $\alpha R$ 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

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

\[ n_i = \theta w_i e_i + s_i \]
\[ d_i = 2w_i \alpha e_i \]
\[ e_i = N - w_i \alpha (1 + R) \]
\[ s_i = 2Sp_2 e_i \]

\[ \theta = \frac{2\alpha \rho kp_1 p_2}{N} \]

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 = $\alpha$ neurons, each having $k$ connections.
- On average, $\rho k$ 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 $p_1p_2$ (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 $\Delta = \frac{1}{2}$ the excitable neurons per gap before annihilation, i.e. $\Delta = \frac{e_i}{(2w_i)}$
- … traversed in $\Delta/\alpha$ 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 \( \rho \) and \( p_1 \) for 1D map
Stability analysis at equilibrium

\( \rho = 0.001 \)

\( \rho = 0.01 \)

\( \rho = 0.05 \)

Slope \(<\,1\)  
Slope \(<\,0\)  
Slope \(<\,-1\)
Stability analysis at equilibrium

\[ N = 3000, \quad k = 90 \]

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<th>\textbf{Slope} \textless -1</th>
<th>\text{Flip bifurcation}</th>
<th>\text{High amplitude oscillations}</th>
<th>\text{Activity saturates}</th>
<th>\text{Burst}</th>
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Fixed point position and slope as function of % long distance connections in network
Maps capture the trends

% Active

Stability

Spikes per 10 ms bin

Spikes per 2 ms bin

CA1 Model (1% connectivity)

CA3 Model (3% connectivity)

1-dim map

(1+R)-dim map

Bursting

Normal

Seizing
Maps capture the trends

Equilibrium loses stability in (1+R)-D map 1-D map

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

(a.k.a. inter-ictal bursts)
Physiological implications

• DG shows SWN connectivity  
  – Specific sclerosis of distantly-projecting hilar neurons  
  – Sprouting of mossy fibres

• Neocortex may behave differently  
  – Different connectivity  
  – Intrinsic bursting neurons (NaP)  

• 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