The impact of complex network structure on seizure activity induced by depolarization block

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Mesoscopic neuronal networks

$\sim 10^5$ neurons per mm$^3$ in primate cortex. Communicate with spikes; connected via synapses.

What determines the ensemble activity of neural networks?

$$\frac{du_i}{dt} = F_i(u_i) + \sum_{j \in \text{Exc}} W_{ij} \phi(u_j) - \sum_{k \in \text{Inh}} W_{ik} \phi(u_k), \quad i = 1, 2, \ldots, N$$

• Single neuron dynamics: $F_i(\cdot)$
• Connectivity structure: $W_{ij}$
• Excitatory and inhibitory neurons: $+/-$

Develop reduced eqn that captures population activity when

• inhibitory neurons are pathological ($F_i$)
• second order connectivity structure ($W_{ij}$).
Spiking neuron model

Morris-Lecar model: (1) simple, realistic ion channel dynamics, (2) enters depolarization block when strong stimulus applied.

\[
C \frac{dV}{dt} = I_{ext} - g_{Na} m(V)(V - E_{Na}) - g_{K} w(t)(V - E_{K}) - g_{Cl}(V - E_{Cl})
\]

\[
\frac{dw}{dt} = \phi \frac{w_{inf}(V) - w}{\tau_w}
\]

\[
m(V) = \frac{1}{2} \left(1 + \tanh \left( \frac{V - V_1}{V_2} \right) \right)
\]

\[
w_{inf}(V) = \frac{1}{2} \left(1 + \tanh \left( \frac{V - V_3}{V_4} \right) \right)
\]
Depolarization block

**Goal:**
Investigate pathological excitatory-inhibitory network dynamics when inh. neurons break down due to depolarization block.

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**Morris-Lecar**

- *Physiological* $E_K$ ($-90$ mV)
- *Pathological* $E_K$ ($-60$ mV)

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**epileptic brain slice**

- **IN**
- **EX**

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Ziburkus et al. ’06
Outline

1. EI network dynamics induced by depolarization block
   - Simulate recurrently connected networks
   - Mean field model
   - Comparison of simulations and mean field analysis

2. Depolization block in complex network structure
   - Second order network motifs
   - Effects of the convergent and chain motifs
   - Generalized mean field model
Simulate recurrently connected networks

Randomly connect $N$ excitatory and $N/4$ inhibitory ML neurons ($N = 3000$) with connection probability $p = 0.01$. For each neuron, simulate

$$
\frac{dV_i}{dt} = F_i(V_i, w_i) + g_i^{exc}(t)(E_{exc} - V_i) + g_i^{inh}(t)(E_{inh} - V_i)
$$

$$
\tau_{exc} \frac{dg_i^{exc}}{dt} = -g_i^{exc} + \sum_{j \in \text{Exc}} J_{ij} W_{ij} \sum_k \delta(t - t_j^k)
$$

$$
\tau_{inh} \frac{dg_i^{inh}}{dt} = -g_i^{inh} + \sum_{j \in \text{Inh}} J_{ij} W_{ij} \sum_k \delta(t - t_j^k)
$$

Record the average firing rate of neurons in exc and inh populations. Compare with mean field analysis.
Mean field: I. Population response

Add high susceptibility to depolarization block to inhibitory neurons

Stimulate unconnected ML neurons \((N = 1000)\) with random spikes

- Excitatory neurons: monotonic response to stimulus
- Inhibitory neurons: non-monotonic response to stimulus

Use these features to develop a mean field model that captures large-scale simulation results.
Mean field: II. Modify Wilson-Cowan Eq

Can we come up with a reduced model that captures large-scale simulations?

Modify Wilson-Cowan eqn:

\[
\frac{dr_e}{dt} = -r_e + \phi_e(J_{ee}r_e - J_{ei}r_i + I_e)
\]
\[
\tau \frac{dr_i}{dt} = -r_i + \phi_i(J_{ie}r_e - J_{ii}r_i + I_i),
\]

- \( r_e/i \): activity of exc/inh populations.
- \( \phi_e/i \): transfer function converts input to output

Make inhibitory transfer function, \( \phi_i \), non-monotonic to capture DB.

\[
\phi_e(x) = \frac{1}{1 + e^{-x}}, \quad \phi_i(x) = \frac{1}{1 + e^{-x}} \cdot \frac{1}{1 + e^{k(x-\theta)}}.
\]
Can ad hoc mean-field model explain network simulations?

Mean-field predicts that network state can be bistable.

Normal state ($b_1$) and seizure state ($b_2$) coexist.

After brief external stimulus, inh neurons enter depolarization block and exc neurons fire at max rate. This corresponds to seizure state ($b_2$).
Non-oscillatory transition

Phase plane

Increase $I_{ext}^E$ →  Decrease $I_{ext}^E$

Bifurcation diagram

Network simulations
Oscillatory transition

E-E coupling increased.

Increase $I_{ext}^E$  \[\rightarrow\]  Decrease $I_{ext}^E$
Dynamics around Bogdanov-Takens

- External input
- Oscillation (osc)
- Seizure (seizure)
- Normal state
- Homoclinic bifurcation (HB, HC)
- Saddle-node bifurcation (SN, BT)
Conclusions, first half

1. Mean field model captures different types of transitions to seizure-like activity that are seen in network model.
   - oscillatory, non-oscillatory, and tonic-clonic transitions
1. EI network dynamics induced by depolarization block
   - Simulate recurrently connected networks
   - Mean field model
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2. Depolization block in complex network structure
   - Second order network motifs
   - Effects of the convergent and chain motifs
   - Generalized mean field model
Second order networks (SONETs)

\( W_{ij} = 1 \) denotes a connection from node \( j \) to \( i \). Else \( W_{ij} = 0 \).

\[ P(W_{ij} = 1) = p. \]

For an Erdős-Rényi graph, all edges are independent:

\[ P(W_{ij} = 1, W_{kl} = 1) = p^2 \]

Second order statistics of \( W_{ij} \) are trivial.

Go beyond E-R: (1) fix connection probability \( p \)
(2) generate \( W_{ij} \); second ord stat equals to prescribed \( \alpha \)'s.

\[ \alpha_{\text{recip}} = \frac{\text{cov}(W_{ij}, W_{ji})}{p^2} \]
\[ \alpha_{\text{conv}} = \frac{\text{cov}(W_{ij}, W_{ik})}{p^2} \]
\[ \alpha_{\text{div}} = \frac{\text{cov}(W_{ij}, W_{kj})}{p^2} \]
\[ \alpha_{\text{chain}} = \frac{\text{cov}(W_{ij}, W_{jk})}{p^2} \]

[Zhao et al '11]
Properties of second order networks: Erdős-Rényi

The Erdős-Rényi random network

\[ N = 20, \ p = 0.3, \ \alpha_{\text{recip}} = -0.1, \ \alpha_{\text{conv}} = 0, \ \alpha_{\text{div}} = 0, \ \alpha_{\text{chain}} = 0 \]

\[ N = 3000, \ p = 0.01, \ \alpha_{\text{recip}} = 0, \ \alpha_{\text{conv}} = 0, \ \alpha_{\text{div}} = 0, \ \alpha_{\text{chain}} = 0 \]
Properties of second order networks: reciprocal

Add reciprocal connections: \( \circlearrowleft \)

- For \( N = 20, p = 0.3, \alpha_{\text{recip}} = 2.0, \alpha_{\text{conv}} = 0, \alpha_{\text{div}} = 0, \alpha_{\text{chain}} = 0 \)
- For \( N = 3000, p = 0.01, \alpha_{\text{recip}} = 3, \alpha_{\text{conv}} = 0, \alpha_{\text{div}} = 0, \alpha_{\text{chain}} = 0 \)
Properties of second order networks: convergent

Add convergent connections:

$N = 20, \ p = 0.3, \ \alpha_{\text{recip}} = 0.1, \ \alpha_{\text{conv}} = 0.5, \ \alpha_{\text{div}} = 0, \ \alpha_{\text{chain}} = 0$

$N = 3000, \ p = 0.01, \ \alpha_{\text{recip}} = 0, \ \alpha_{\text{conv}} = 3, \ \alpha_{\text{div}} = 0, \ \alpha_{\text{chain}} = 0$
Properties of second order networks: divergent

Add divergent connections:

\[ N = 20, \ p = 0.3, \ \alpha_{\text{recip}} = -0.1, \ \alpha_{\text{conv}} = 0, \ \alpha_{\text{div}} = 0.5, \ \alpha_{\text{chain}} = 0 \]

\[ N = 3000, \ p = 0.01, \ \alpha_{\text{recip}} = 0, \ \alpha_{\text{conv}} = 0, \ \alpha_{\text{div}} = 3, \ \alpha_{\text{chain}} = 0 \]
Properties of second order networks:
no chains

Add convergent and divergent connections, reduce chains:

\[ N = 20, p = 0.4, \alpha_{\text{recip}} = -0.9, \alpha_{\text{conv}} = 0.3, \alpha_{\text{div}} = 0.4, \alpha_{\text{chain}} = -0.3 \]

\[ N = 3000, p = 0.01, \alpha_{\text{recip}} = 0, \alpha_{\text{conv}} = 3, \alpha_{\text{div}} = 3, \alpha_{\text{chain}} = -0.9 \]
Properties of second order networks: chains

Add convergent and divergent connections with chains:

$N = 20, \ p = 0.3, \ \alpha_{recip} = 1.0, \ \alpha_{conv} = 0.3, \ \alpha_{div} = 0.3, \ \alpha_{chain} = 0.3$

$N = 3000, \ p = 0.01, \ \alpha_{recip} = 0, \ \alpha_{conv} = 3, \ \alpha_{div} = 3, \ \alpha_{chain} = 3$
Previous results

Chain motifs

Linear theory works!

- When on linear regime of transfer function, chains have strongest influence on synchrony [Zhao et al ’11, Nykamp et al ’16].
- Increase spike-time correlations (linear response theory) [Hu et al ’13].

Convergent motifs

- Reduce network synchrony due to heterogeneity. [Zhao et al ’11]
- Promote synchrony in low activity regime. [Roxin ’11]

Nonlinearity of transfer function matters!
SONETs and degrees

in-degree $d_{\text{in}}$, out-degree $d_{\text{out}}$

normalized in- and out-degree:

$$x = \frac{d_{\text{in}}}{E(d_{\text{in}})}, \quad y = \frac{d_{\text{out}}}{E(d_{\text{out}})}$$

SONET statistics are variances of the degree distribution:

$$\alpha_{\text{conv}} \approx \var(x) \quad \alpha_{\text{div}} \approx \var(y) \quad \alpha_{\text{chain}} \approx \cov(x, y)$$

$\alpha_{\text{conv}} > 0 \quad \alpha_{\text{div}} > 0 \quad \alpha_{\text{chain}} < 0 \quad \alpha_{\text{chain}} > 0$
A rate equation

Given

- a postsynaptic neuron with in-degree $x$
- a presynaptic neuron with out-degree $\tilde{y}$

Connection probability is proportional to $x\tilde{y}$.

Let $r(x, y, t)$ be firing rate of neuron with degree $(x, y)$.

Get rate equation

$$\frac{dr}{dt}(x, y, t) + r(x, y, t) = \Phi \left( \int Jx\tilde{y}\rho(\tilde{x}, \tilde{y})r(\tilde{x}, \tilde{y}, t) d\tilde{x}d\tilde{y} + I \right)$$

Coupling strength from presynaptic degree $(\tilde{x}, \tilde{y})$ onto postsynaptic degree $(x, y)$ is $Jx\tilde{y}$. 
Generalized equation - Derivation

The dynamics of single neuron firing rate is given by

$$\frac{dr}{dt}(x, y, t) + r(x, y, t) = \phi \left( \int Jx\tilde{y}\rho(\tilde{x}, \tilde{y})r(\tilde{x}, \tilde{y}, t)d\tilde{x}d\tilde{y} + I \right)$$

Define population synaptic activity $h$

$$S(t) = \int yr(x, y, t)\rho(x, y)dxdy$$

Then,

$$\frac{dr}{dt} + r = \phi (JxS(t) + I)$$

Multiply by $y\rho(x, y)$ and integrate to obtain generalized eqn

$$\frac{dS(t)}{dt} + S(t) = \int y\rho(x, y)\phi(JxS(t) + I)dxdy.$$
Linear term depends on chain motif

\[
\frac{dS(t)}{dt} + S(t) = \int y \rho(x, y) \phi(JxS(t) + l) dxdy
\]

Linear term: covariance between in and out degree ($\alpha_{\text{chain}}$)

\[
JS\phi' \int xy \rho(x, y) dxdy = J(1 + \alpha_{\text{chain}}) S\phi'
\]

Result: robust dependence on $\alpha_{\text{chain}}$

Effect of convergence $\alpha_{\text{conv}}$ in higher-order terms
⇒ higher-order derivatives of $\phi$
⇒ nonlinearity shape matters
Generalized equation - EI network

If in-degree depends on out-degree ($\alpha_{\text{chain}} \neq 0$), the generalized eqn has four synaptic variables, $S_{ee}, S_{ie}, S_{ei}, S_{ii}$, representing each edge.

Consider reduced eqns: assume in-degree is independent of out-degree ($\alpha_{\text{chain}} = 0$). The population rate activity

$$S_k(t) = \int \rho(x_k) r(x_k, t) dx_k$$

satisfies

$$\frac{dS_e}{dt} + S_e = \int \rho_e(x_e) \phi_e(J_{ee}x_{ee}S_e - J_{ei}x_{ei}S_i + I_e) dx_e$$

$$\frac{dS_i}{dt} + S_i = \int \rho_i(x_i) \phi_i(J_{ie}x_{ie}S_e - J_{ii}x_{ii}S_i + I_i) dx_i.$$ 

where $\rho(\cdot)$ is in-degree distribution. [Nykamp et al ’16; Roxin ’11]
Convergent motifs in EI network

Consider convergent motifs across the EI network.

\[
\alpha_{i,ee}^{\text{conv}} > 0
\]

Non-monotonic response of inh neurons leads to strong dependence on \(\alpha_{i,ee}^{\text{conv}}\).

Heterogeneity of inh synapses disrupts synchrony in high activity regime.
Simulations: \( i \) facilitates seizure onset

Near seizure, inh neurons with
- high exc in-degree enter DB,
- low exc in-degree have weak inh activity

\[ \Rightarrow \text{Overall inh activity reduced.} \]

\( \alpha_{i,ee}^{\text{conv}} > 0 \) facilitates transition to seizure state.
Simulations: $\implies$ favors non-osc transition

Heterogeneous inh synaptic inputs disrupt EI oscillations at high activity regime.

$\alpha_{\text{conv}}$ suppresses oscillations near the transition.
Saddle-node and homoclinic bifurcations occur at reduced $I_e$
Global bifurcation

Oscillatory regime pushed away near the transition.
Analytical results

Assume

1. the E-I coupling is strong ($J_{ei} J_{ie} > J_{ee} J_{ii}$) and
2. $\Phi''_i, \Phi'''_i, \Phi''_e, \Phi'''_e < 0$ at high activity regime.

- $\alpha_{i,ee}^{\text{conv}}$ facilitates a saddle-node and a Hopf bifurcation.
  (Red $< 0$, Blue $> 0$)

\[
\det L_{\alpha_{i,ee}^{\text{conv}}} = \det L_0 + \alpha_{i,ee}^{\text{conv}} \left[ \frac{1}{\tau} J_{ei} \Phi'_e \cdot J_{ie}^2 S_e \Phi''_i + \frac{1}{2} J_{ie}^2 J_{ii} S_e^2 \Phi'''_i \\
+ \frac{1}{2} J_{ie}^2 S_e^2 \Phi''_i \Phi'_e (J_{ee} J_{ii} - J_{ei} J_{ie}) \right]
\]

\[
\text{tr} L_{\alpha_{i,ee}^{\text{conv}}} = \text{tr} L_0 + \alpha_{i,ee}^{\text{conv}} \cdot \frac{1}{2\tau} J_{ie}^2 J_{ii} S_e^2 (\Phi'''_i). \]

- $\alpha_{e,ii}^{\text{conv}}$ favors non-oscillatory transition to seizure.

\[
\text{tr} L_{\alpha_{e,ii}^{\text{conv}}} = \text{tr} L_0 + \alpha_{e,ii}^{\text{conv}} \cdot \frac{1}{2} J_{ee} J_{ei}^2 S_i^2 \Phi''_e. \]
Conclusions

1. Mean field model captures different types of transitions to seizure-like activity that are seen in network model.
   - oscillatory, non-oscillatory, and tonic-clonic transitions

2. Influence of network structure on these transitions
   - Nonlinearity of transfer function leads to strong dependence on convergent motifs
   - Heterogeneous synaptic inputs can suppress synchrony.
   - Generalized equation can capture such effects.
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Tonic-clonic transition

Transition occurs when $E_k$ recovered toward physio value.

Simulations

Jensen, Yaari ’97

TONIC (patho $E_k$) −−−→ CLONIC (physio $E_k$)
Chains can modulate the effect of $\alpha^\text{chain}$.

Correlate inh neuron's out-degree with its exc in-degree.

Correlated out-degree can amplify/suppress effects of $\alpha^\text{conv}_{i,ee}$. 

\[ \alpha^\text{chain}_{i.e} > 0 \quad \alpha^\text{chain}_{i.e} < 0 \]
Chains can modulate the effect of $\alpha_{\text{chain}}$. 

Correlate exc neuron’s out-degree with its inh in-degree.

Correlated out-degree accelerates/delays seizure onset.