Synaptic Volatility, Inhibitory Plasticity and the Synaptic Trace Theory of Memory

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Plan of the Lecture

First 2 hours (talk + blackboard):


Last hour – Implications of the balanced regime for memory function (talk):

Outline

• Synaptic dynamics *in vivo*: chronic spine imaging

• Implications for learning (*and memory storage*)

• Conclusions
“The first step in this neural schematizing is a bald assumptions about the structural changes that make lasting memories possible. [...] The assumption, in brief, is that a growth process accompanying synaptic activity makes the synapse more readily traversed. [...] To account for the permanence [of the memory] some structural change seems necessary [...]”.

Donald O. Hebb (1949)

“With both explicit and implicit memory there are stages in memory that are encoded as changes in synaptic strength and that correlate with the behavioral phases of short- and long-term memory [...] whereas the long-term synaptic changes involve activation of gene expression, new protein synthesis, and the formation of new connections”.

Eric R. Kandel (2001)

«[…] les esprits qui sortent de la glande […] ont la force […] de plier et disposer diversement les petits filets qu'ils rencontrent […] en sorte qu'ils y tracent aussi des figures, qui se rapportent à celles des objets; non pas toutefois si aisément du premier coup […] mais peu à peu de mieux en mieux, selon que leur action […] est plus de fois réitérée. Ce qui est cause que ces figures ne s'effacent pas non plus si aisément […]. Et c'est en quoi consiste la mémoire. »

René Descartes (1664)
Synaptic Ghosts of Things Past

stimulus-dependent activity

activity-dependent synaptic plasticity

stabilization of structural changes
Spines: Basic Facts

- >90% of excitatory synapses terminate on spines
- Spine volume is a proxy of the synaptic efficacy

(Harris, 1989)

(Arellano et al., 2007)

(Matsuzaki et al., 2005)
Spines: Experience-driven Dynamics

(Xu et al., 2009)
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(Xu et al., 2009)
**Spines: 'Ongoing' Dynamics**

**The Dataset**
- 6 mice
- 8 neurons
- 3688 spines
- 6 time points (4-days interval)

(Loewenstein et al., 2011; Loewenstein et al., 2015)
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- 8 neurons
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Spines: 'Ongoing' Dynamics

(Loewenstein et al., 2011; Loewenstein et al., 2015)
Spines: 'Ongoing' Dynamics

The Dataset
6 mice
8 neurons
3688 spines
6 time points (4-days interval)

# of spines (on a given neuron) is approximately constant across sessions
(Loewenstein et al., 2011; Loewenstein et al., 2015)
Spines: 'Ongoing' Dynamics

(Loewenstein et al., 2011)
Spines: 'Ongoing' Dynamics

- spines' size distribution is well fitted by a log-normal distribution, and approximately constant across sessions
- spines' size distribution is approximately constant across neurons

(Loewenstein et al., 2011)
Spines: 'Ongoing' Dynamics

- Spines' size distribution is well fitted by a log-normal distribution, and approximately constant across sessions.
- Spines' size distribution is approximately constant across neurons.

Ongoing spine dynamics preserve the gross statistical features of synaptic connectivity (E→E)

(Loewenstein et al., 2011)
Ephemeral Cortical Circuits

.. the fine structure, however, appears to undergo dramatic changes..

Most spines present in the first imaging day are no longer present after 20 days (Loewenstein et al., 2015)

70% of the stable spines changed their size by at least a factor 2 within 20 days (Loewenstein et al., 2011)
Ephemeral Cortical Circuits

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What is the effect of such a massive structural re-organization on the patterns of neuronal activity exhibited by the network?
Mechanisms for Stability of Long-term Memories

A Biologically-Constrained Model Network

N=40,000 (80% E – 20% I) LIF Neurons
Random connectivity
Log-normal distribution of synaptic efficacies
E→E connectivity from spine data

External inputs were adjusted to reproduce experimentally observed firing rates:

Exc: ~1Hz – Inh: ~5Hz

Experimentally observed spine data were used to simulate network re-organization

(Avermann et al., 2012)
A Biologically-Constrained Model Network

- Temporally irregular spiking resembling Poisson process.
A Biologically-Constrained Model Network

- Temporally irregular spiking resembling Poisson process.
- Right-skewed, long-tailed distributions of average rates.

(Roxin et al., 2011)
Effects of $E \rightarrow E$ Volatility

Experimentally observed spine data were used to simulate network reorganization.
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Effects of $E \rightarrow E$ Volatility

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Effects of $E \rightarrow E$ Volatility

Experimentally observed spine data were used to simulate network reorganization.
Rewiring

![Bar chart showing correlation]

E → E (50%)
Rewiring

- E→E (50%)
- E→I (18.75%)
- I→E (25%)
- I→I (6.25%)
Patterns of ongoing activity are robust against changes in excitatory synapses while being very sensitive to changes in inhibitory synapses.
A Simple Intuitive Explanation
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The activity will NOT change if $w_1 = w_2$ or $v_1 = v_2$

$w_1v_2 = w_2v_1$
The activity will NOT change if $w_1 = w_2$ or $v_1 = v_2$

$w_1 v_2 = w_2 v_1$

\[
\sigma_{EE}^2 = c_{EE} \cdot N_E \left( \langle w_{EE}^2 \rangle \langle v_E^2 \rangle - c_{EE} \langle w_{EE} \rangle^2 \langle v_E \rangle^2 \right)
\]

\[
\sigma_{EI}^2 = c_{EI} \cdot N_I \left( \langle w_{EI}^2 \rangle \langle v_I^2 \rangle - c_{EI} \langle w_{EI} \rangle^2 \langle v_I \rangle^2 \right)
\]

$$\frac{\sigma_{EE}^2}{\sigma_{EI}^2} \approx 0.04$$

(Gentet et al., 2010; Avermann et al., 2012)
A Simple Intuitive Explanation

The activity will NOT change if $w_1 = w_2$ or $\nu_1 = \nu_2$

$$\sigma_{EE}^2 = c_{EE} \cdot N_E \left( \langle w_{EE}^2 \rangle \langle \nu_E^2 \rangle - c_{EE} \langle w_{EE} \rangle^2 \langle \nu_E \rangle^2 \right)$$

$$\sigma_{EI}^2 = c_{EI} \cdot N_I \left( \langle w_{EI}^2 \rangle \langle \nu_I^2 \rangle - c_{EI} \langle w_{EI} \rangle^2 \langle \nu_I \rangle^2 \right)$$

$$w_1 \nu_2 = w_2 \nu_1$$

$$4 \text{ Hz}^2$$

$$80 \text{ Hz}^2$$

$$\frac{\sigma_{EE}^2}{\sigma_{EI}^2} \approx 0.04$$

(Gentet et al., 2010; Avermann et al., 2012)
A Possible Mechanism for Learning

(a) Connectivity

(b) Firing rate vs neuron number

(f) Spines vs Formation and Elimination
   - General control
   - Shaping control
   - Activity control
   - Training (>10 successes)

*** Significant difference
A Possible Mechanism for Learning

(a) Connectivity

(b) Firing rate and neuron number

Graph showing Spines (%) with different conditions:
- General control
- Shaping control
- Activity control
- Training (>10 successes)

Legend:
- Formation
- Elimination

Significance levels:
- ***
A Possible Mechanism for Learning

(a) Connectivity

(b) Firing rate [Hz]

(f) Spines (%)
A Possible Mechanism for Learning

a
- base
- $f = 0.2$
- $f = 1.0$

Connectivity

b
- Neuron number vs. firing rate [Hz]

f
- Spines (%)
- General control
- Shaping control
- Activity control
- Training (>10 successes)

Formation vs. Elimination

***
A Possible Mechanism for Learning

(a) Connectivity and firing rate distributions for different frequencies:
- **base**: Normal connectivity and firing rates.
- **f = 0.2**: Moderate changes in connectivity and firing rates.
- **f = 1.0**: Significant changes in connectivity and firing rates.

(b) Firing rate distributions for neuron number:
- Neuron number: 0, 4, 8, 12, 16, 20.
- Firing rate [Hz]: 0, 4, 8, 12, 16, 20.

Graph showing spines (%):
- Differences in spine formation and elimination across different conditions.
- General control, Shaping control, Activity control, Training (>10 successes).

Significance indicated with ***.
A Possible Mechanism for Learning

(a) 
- base
- f = 0.2
- f = 1.0

C
- inhibition (simulations)
- excitation (simulations)

neuron number

firing rate [Hz]
A Possible Mechanism for Learning

**ongoing plasticity**

![Graph showing ongoing plasticity](image1)

**learning-like plasticity**

![Graph showing learning-like plasticity](image2)
\[ \sigma_E^2 = \sigma_{EE}^2 + \sigma_{EI}^2 = N \cdot O(1) \]
The Balanced State

\[
\begin{align*}
\sigma_E^2 & = \sigma_{EE}^2 + \sigma_{EI}^2 = N \cdot O(1) \\
\frac{\sigma_E}{\mu_E} & = O\left(\frac{1}{\sqrt{N}}\right)
\end{align*}
\]
The Balanced State

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The Balanced State

\[
\sigma_E^2 = \sigma_{EE}^2 + \sigma_{EI}^2 = N \cdot O(1)
\]

\[
\mu_E = N \left[ \mu_E^{(ext)} + \langle w_{EE} \rangle \langle \nu_E \rangle - \langle w_{EI} \rangle \langle \nu_I \rangle \right]
\]

\[
O\left(\frac{1}{\sqrt{N}}\right)
\]

\[
\frac{\sigma_E}{\mu_E} = O(1)
\]
Under very general conditions, activity will evolve to a steady state where the total excitation and inhibition nearly cancel each other (balanced state). 

(van Vreeswijk & Sompolinsky, 1996; 1998)
Transiently Unbalanced Networks

\[ \mu_E = N \cdot \left[ \mu_E^{(ext)} + \langle w_{EE} \rangle \langle \nu_E \rangle - \langle w_{EI} \rangle \langle \nu_I \rangle \right] \]

\[ \mu_I = N \cdot \left[ \mu_I^{(ext)} + \langle w_{IE} \rangle \langle \nu_E \rangle - \langle w_{II} \rangle \langle \nu_I \rangle \right] \]
Transiently Unbalanced Networks

\[ \mu_E = N \cdot \left[ \mu^{(ext)}_E + \langle w_{EE} \rangle \langle \nu_E \rangle - \langle w_{EI} \rangle \langle \nu_I \rangle \right] \]

\[ \mu_I = N \cdot \left[ \mu^{(ext)}_I + \langle w_{IE} \rangle \langle \nu_E \rangle - \langle w_{II} \rangle \langle \nu_I \rangle \right] \]

\[ \mu^{(p)}_E = N \cdot \left[ \mu^{(ext)}_E + f \gamma \langle w_{EE} \rangle \langle \nu^{(p)}_E \rangle + (1 - f) \langle w_{EE} \rangle \langle \nu^{(0)}_E \rangle - \langle w_{EI} \rangle \langle \nu_I \rangle \right] \]

\[ \mu^{(0)}_E = N \cdot \left[ \mu^{(ext)}_E + f \langle w_{EE} \rangle \langle \nu^{(p)}_E \rangle + (1 - f) \langle w_{EE} \rangle \langle \nu^{(0)}_E \rangle - \langle w_{EI} \rangle \langle \nu_I \rangle \right] \]
Transiently Unbalanced Networks

\[ \mu_E = N \cdot [\mu_E^{(\text{ext})} + \langle w_{EE} \rangle \langle \nu_E \rangle - \langle w_{EI} \rangle \langle \nu_I \rangle] \]

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\[ \mu_E^{(p)} = N \cdot [\mu_E^{(\text{ext})} + f \gamma \langle w_{EE} \rangle \langle \nu_E^{(p)} \rangle + (1 - f) \langle w_{EE} \rangle \langle \nu_E^{(0)} \rangle - \langle w_{EI} \rangle \langle \nu_I \rangle] \]

\[ \mu_E^{(0)} = N \cdot [\mu_E^{(\text{ext})} + f \langle w_{EE} \rangle \langle \nu_E^{(p)} \rangle + (1 - f) \langle w_{EE} \rangle \langle \nu_E^{(0)} \rangle - \langle w_{EI} \rangle \langle \nu_I \rangle] \]

\[ \mu_E^{(p)} - \mu_E^{(0)} = N \cdot [(\gamma - 1) f \langle w_{EE} \rangle \langle \nu_E^{(p)} \rangle] = O(N) \]
Transiently Unbalanced Networks

(a) Connectivity diagrams for different conditions:
- **base**
- **f = 0.2**
- **f = 1.0**

(b) Histograms of neuron firing rates for different conditions:
- **firing rate [Hz]**
- **neuron number**

The diagrams illustrate changes in network connectivity and firing rate distributions under varying conditions.
Where Is Learned Information Stored?

(Xu et al., 2009)
Conclusions

- Quantitative theory relating changes in synaptic connectivity to changes in patterns of ongoing activity. (stability of neuronal representations?)

- Considering changes that preserve the overall distribution of connections, inhibitory plasticity is both necessary and sufficient for large-scale changes in network activity. (functional role of synaptic volatility?)

- Transient, local changes in statistics of the E→E connectivity could drive activity-dependent inhibitory plasticity. (role of inhibitory plasticity in learning/memory?)
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• Transient, local changes in statistics of the E\(\rightarrow\)E connectivity could drive activity-dependent inhibitory plasticity. (role of inhibitory plasticity in learning/memory?)

Next (on the blackboard)

Storing a large number of memories in biologically-constrained model Networks – Mean-field analysis and estimate of the storage capacity