Short-term synaptic plasticity, inhibitory interneurons, and the response of cortical circuits to thalamic inputs

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With:
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Erika Fanselow, Univ. of Pittsburgh – experiments
Kris Richardson, Brown Univ. - experiments
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LTS cells in the local cortical circuit

RS and FS neurons, but not LTS neuron, receive excitatory thalamic input.
Content

1. Dynamics of fast-spiking neurons.
3. Facilitation and the prevention of overactivation.
4. Tsodyks-Markram model of depression and facilitation.
5. RS-LTS-FS networks with Tsodyks-Markram synaptic dynamics.
Effects of d- and Na\(^+\) currents on firing patterns of FS neurons

**Na\(^+\) current, \(I_{Na}\)**

\[
I_{Na} = g_{Na} m_{\infty}^3(V) \times (V - V_{Na})
\]

\[
dh/dt = \left[ h_{\infty}(V) - h \right] / \tau_h(V)
\]

\(\theta_m\) depolarized: small window current

**Window Na\(^+\) Current:**

steady state value

\[
I_{Na}^{\text{window}} = g_{Na} m_{\infty}^3(V) h_{\infty}(V) \times (V - V_{Na})
\]
Small window current

$\theta_m = -24 \, \text{mV}$
Large window current

$\theta_m = -28 \text{ mV}$
Short-term synaptic plasticity

RS-to-LTS synapses facilitate. LTS-to-RS synapses depress.

Beierlein, Gibson and Connors, 2003

Frequency-dependent disynaptic inhibition (FDDI)

Berger et al., 2010; also, Silberberg and Markram, 2007; Kapfer et al., 2007.
Possible role of LTS neurons

Silberberg and Markram: “The involvement in feedback self-inhibition suggests that this pathway is important in preventing overactivation of cortical pyramidal cells, which may be important in the prevention of epilepsy”.

Correlation was found between selective loss of hippocampal somatostatin-positive neurons and epileptic states (Buckmaster and Jongen-Relo, 1999; Cossart et al., 2001).

Result or cause?

Question: Is this role limited by the LTS-to-RS synaptic depression?
Theoretical treatment: background

Presynaptic side: independent release sites

\( n \) – number of release sites.

\( q \) – quantum value.

\( x \) – fraction of release sites with vesicles.

\( u \) – conditional probability of release.

Average amount of transmitter release: \( T = nqxu \)

Postsynaptic side:

\[
\frac{ds}{dt} = k_f T (1 - s) \delta (t - t_i) - k_r s
\]

Depletion model of Depression: dynamics of $x$


“During” a spike:  \[ x_{n+}^+ = x_n^- (1 - u_n^+) \]

Between spikes:  \[ x_{n+1}^- = 1 - (1 - x_n^+) e^{-\Delta t/\tau_r} \]

After a long quiescent period,  \[ x_1^- = 1 \]
Ca$^{2+}$ binding model for facilitation: dynamics of $u$


A Ca$^{2+}$ sensor needs to bind to 4 Ca$^{2+}$ ions:

$$D_j + Ca \frac{k^+}{k^-} B_j \quad j = 1, 2, 3, 4.$$ 

$$\sigma_j = E[B_j]$$

$$\frac{d\sigma_j}{dt} = -(k^- + k^+ Ca)\sigma_j + k^+ Ca \quad j = 1, 2, 3, 4.$$ 

Release probability: $\sigma_1 \sigma_2 \sigma_3 \sigma_4$
Tsodyks-Markram model  


Only one $\sigma$ controls the conditional probability of release.

We consider a spike train after a long quiescent period. $n$ is the spike number.

During a spike, $k^+Ca \gg k^-$

$$\sigma_n^+ \approx 1 - (1 - \sigma_n^-)e^{-k^+Ca\Delta t_s}$$

$$\sigma_1^- = 0$$

$$U \equiv \sigma_1^+ = 1 - e^{-k^+Ca\Delta t_s}$$

$$u_n \equiv \sigma_n^+ = 1 - (1 - \sigma_n^-)(1 - U)$$

$$\sigma_{n+1}^- = \sigma_n^+e^{-T/\tau_f}, \quad \tau_f = 1/k^-$$

$$u_{n+1} = u_ne^{-T/\tau_f} + U\left(1 - u_ne^{-T/\tau_f}\right)$$

The transmitter release is: $T_n = nqx_n^-u_n^+$
The rate model

\[
\frac{ds}{dt} = -\frac{s}{\tau_s} + uxM
\]

\[
M = \beta \left[ I_{\text{ext}} + I_{\text{syn}} - \theta \right]_+
\]

\[
\frac{dx}{dt} = \frac{1 - x}{\tau_r} - uxM
\]

\[
\frac{du}{dt} = \frac{U - u}{\tau_f} + U(1 - u)M
\]

Wilson and Cowan 1973; Shriki, Hansel and Sompolinsky 2003; Tsodyks, Pawelzik and Markram, 1998;

- \(s\) – synaptic activity.
- \(M\) – firing rate of neuronal population.
- \(x\) – fraction of vesicles available for release.
- \(u\) – conditional probability of release.
Firing rates

\[ M_R = \beta_R \left[ I_R(t) + g_{RR}s_{RR} - g_{RL}s_{RL} - g_{RF}s_{RF} - \theta_R \right]_+ \]

\[ M_L = \beta_L \left[ g_{LR}s_{LR} - g_{LF}s_{LF} - \theta_L \right]_+ \]

\[ M_F = \beta_F \left[ I_F(t) + g_{FR}s_{FR} - g_{FL}s_{FL} - g_{FF}s_{FF} - \theta_F \right]_+ \]
<table>
<thead>
<tr>
<th>Synapse</th>
<th>$U$</th>
<th>$\tau_r$ (ms)</th>
<th>(ms) $\tau_f$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS-to-RS (RR)</td>
<td>0.21</td>
<td>463</td>
<td></td>
</tr>
<tr>
<td>RS-to-LTS (LR)</td>
<td>0.09</td>
<td></td>
<td>670</td>
</tr>
<tr>
<td>LTS-to-RS (RL)</td>
<td>0.3</td>
<td>1250</td>
<td></td>
</tr>
</tbody>
</table>

Wang, Markram et al., 2006.

Reciprocally-connected RS-LTS neuronal populations

Steady state.

The effect of LTS neurons on the shape of the $M_R-I_R$ curve is strongest just above LTS firing threshold.

For large $I_R$,

$$M_R \approx \beta_R \left( I_R - \theta_R - g_{RL} \frac{\tau_{s,RL}}{\tau_{r,RL}} \right)$$
At high LTS firing rates $M_L$, the synaptic input from LTS neurons to RS neurons is constant, because

$$PSP \propto \frac{1}{M_L}$$

(Tsodyks and Markram, 1997).
Dynamics: response to step input.

\[ \tau_{r,RL} > \tau_{f,LR} \]

\[ \tilde{I}_R(t) = I_R \Theta(t) \]
Networks with RS-to-RS synapses

RS-to-RS synapses depress.

For large $I_R$,

$$M_R \approx \beta_R \left( I_{ext} - \theta_R - g_{RL} \frac{\tau_{s,RL}}{\tau_{r,RL}} + g_{RR} \frac{\tau_{s,RR}}{\tau_{r,RR}} \right)$$
Dynamics: response to step input.
Fast oscillations

B

\[ M_R \]

SNP \quad HB

- stable FP
- unstable FP
- stable LC

C

\[ I_R \]

FP

LC

D

\[ f (\text{Hz}) \]

\[ g_{RR} \]

\[ M (\text{Hz}) \]

\[ t (\text{ms}) \]

- \( M_R \)
- \( M_L \)
Reciprocally-connected RS-FS neuronal populations

- FS neurons receive thalamic input.
- RS-to-FS synapses depress.
- For large firing rates, the FS population decreases the firing rate of the RS neuron by a constant value.

\[ M_{F,\text{max}} \approx \beta_F \left( I_F + g_{FR} \tau_{s,FR} / \tau_{r,FR} - \theta_F \right) \]
\[ s_{RF,\text{max}} = \tau_{s,RF} U_{RF} M_{F,\text{max}} / \left( 1 + \tau_{r,RF} U_{RF} M_{F,\text{max}} \right) \]
\[ M_R = \beta_R \left( I_R + g_{RR} \tau_{s,RR} / \tau_{r,RR} - g_{RF} s_{RF,\text{max}} - \theta_R \right) \]
Dynamics: response to step input.

Window of opportunity (D. Simons, H. Swadlow...)
RS-LTS-FS network

- Slow network oscillations with time scale of short-term synaptic plasticity.
- More active state: LTS neurons are silent.
- Less active state: FS neurons are silent.
Experimental results

Golanov and Reis, J. Physiol. (Lond.), 1996.
Reduced network

- No synaptic depression.
- RS-to-LTS synaptic facilitation: one slow variable.
Fast-slow analysis

Slow equation

\[ \frac{du_{LR}}{dt} = \frac{U_{LR} - u_{LR}}{\tau_{f,LR}} + U_{LR} \left(1 - u_{LR}\right)M_{R} \]

Limit: \( \tau_{f,LR} \to \infty, U_{LR} \to 0, C = \tau_{f,LR} U_{LR} \) constant.

To the first order in \( 1/\tau_{f,LR} \),

\[ \frac{du_{LR}}{dt} = \frac{1}{\tau_{f,LR}} \left[-u_{LR} \left(1 + CM_{R}\right) + CM_{R}\right] \]
Fast-slow analysis

\[ \frac{du_{LR}}{dt} = 0 \]

\[ u_{LR} = CM_R / (1 + CM_R) \]
Phase diagram

M_L=0

M_L>0, M_F>0

M_F=0

\( u^+ = u^- \)

\( (u^+, M_R^+) \) touches the slow nullcline

\( (u^-, M_R^-) \) touches the slow nullcline
Conclusions

- In an RS-LTS network model, LTS neurons:
  - Reduce the RS firing rate $M_R$ at steady-state by a constant amount at large $M_R$.
  - Affect the shape of the $M_R$ - $I_R$ curve mainly just above LTS firing threshold.
- FS neurons reduce $M_R$ at steady-state by a constant amount at large $M_R$ as well, but for a different reason.
- Both LTS and RS neurons reduce the RS activity after an initial period, and then the RS activity rebounds.
- An RS-LTS-FS network may exhibit slow oscillations, during which FS (resp. LTS) neurons fire during the more (resp. less) active state of the RS neuronal population.
- Fast-slow analysis reveals that these oscillations exist in a wide regime of $I_R$ and a narrow regime of $I_F$. 