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

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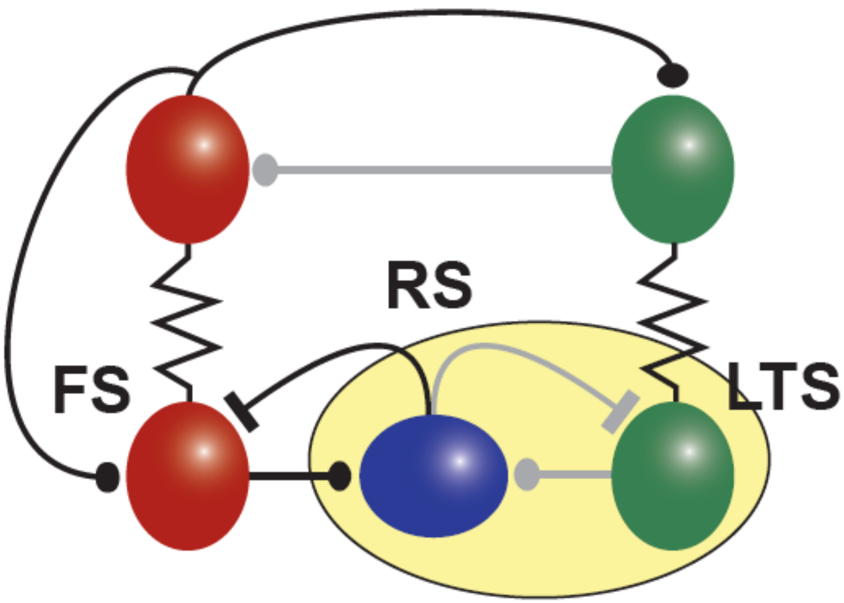
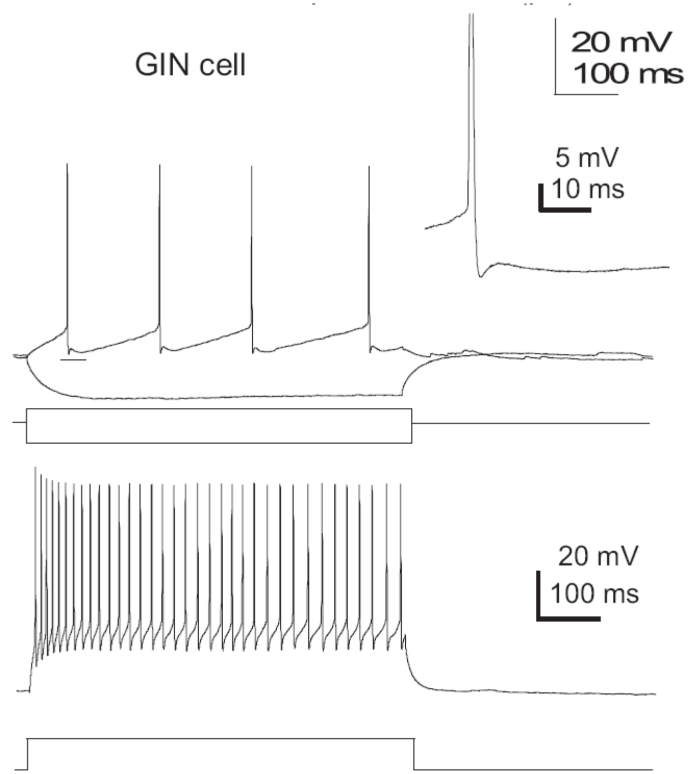
With:
Itay Hayut, BGU – theory
Erika Fanselow, Univ. of Pittsburgh – experiments
Kris Richardson, Brown Univ. - experiments
Barry Connors, Brown Univ. - experiments

LTS cells in the local cortical circuit



Beierlein, Gibson and Connors, 2003.



Fanselow, Richardson and Connors, 2008.

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

Content

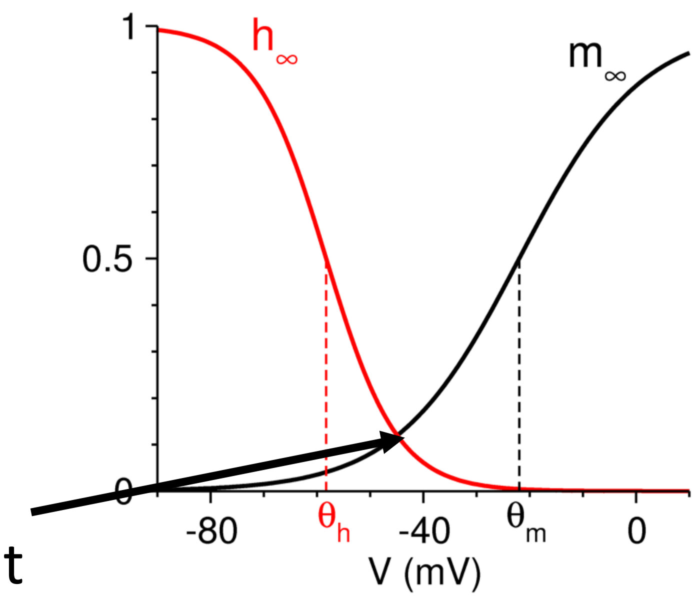
1. Dynamics of fast-spiking neurons.
2. Short-term synaptic plasticity of RS-to-LTS and LTS-to-RS synapses.
3. Facilitation and the prevention of overactivation.
4. Tsodyks-Markram model of depression and facilitation.
5. RS-LTS-FS networks with Tsodyks-Markram synaptic dynamics.
6. Experimental results on RS-to-LTS and LTS-to-RS synapses.
7. Revised model of LTS-to-RS synapses.

Effects of d- and Na^+ currents on firing patterns of FS neurons

Golomb, Doner, Shacham, Shlosberg, Amitai and Hansel, 2007.

Na^+ current, I_{Na}

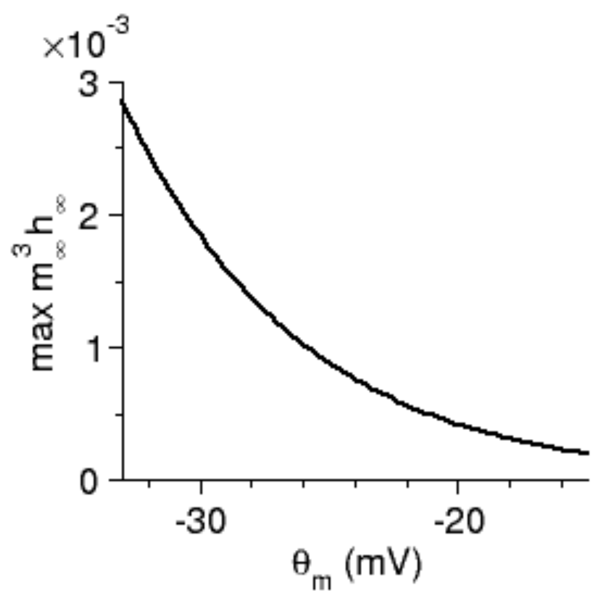
$$I_{Na} = g_{Na} m_\infty^3(V) h \times (V - V_{Na})$$
$$dh/dt = \left[h_\infty(V) - h\right]/\tau_h(V)$$



θ_m depolarized: small window current

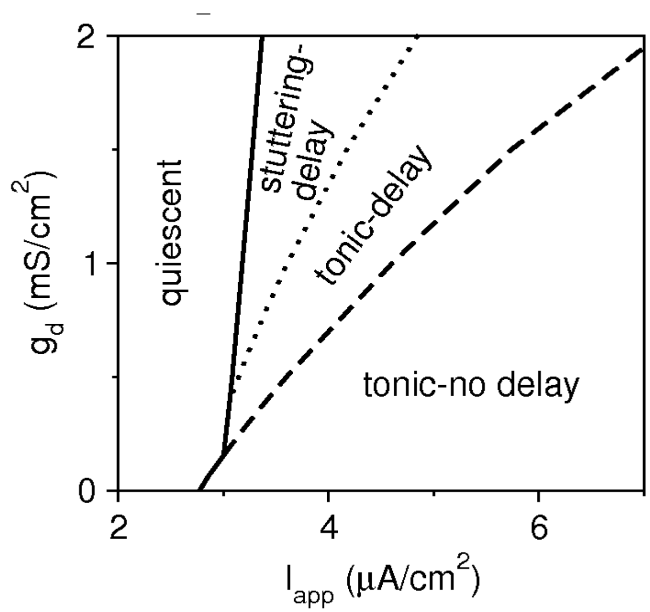
Window Na^+ Current:
steady state value

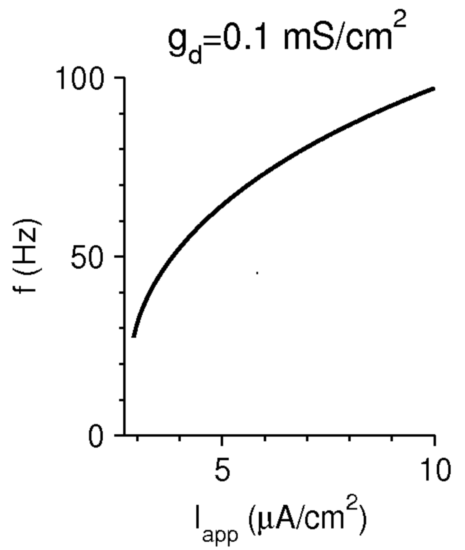
$$I_{Na}^{window} = g_{Na} m_\infty^3(V) h_\infty(V) \times (V - V_{Na})$$

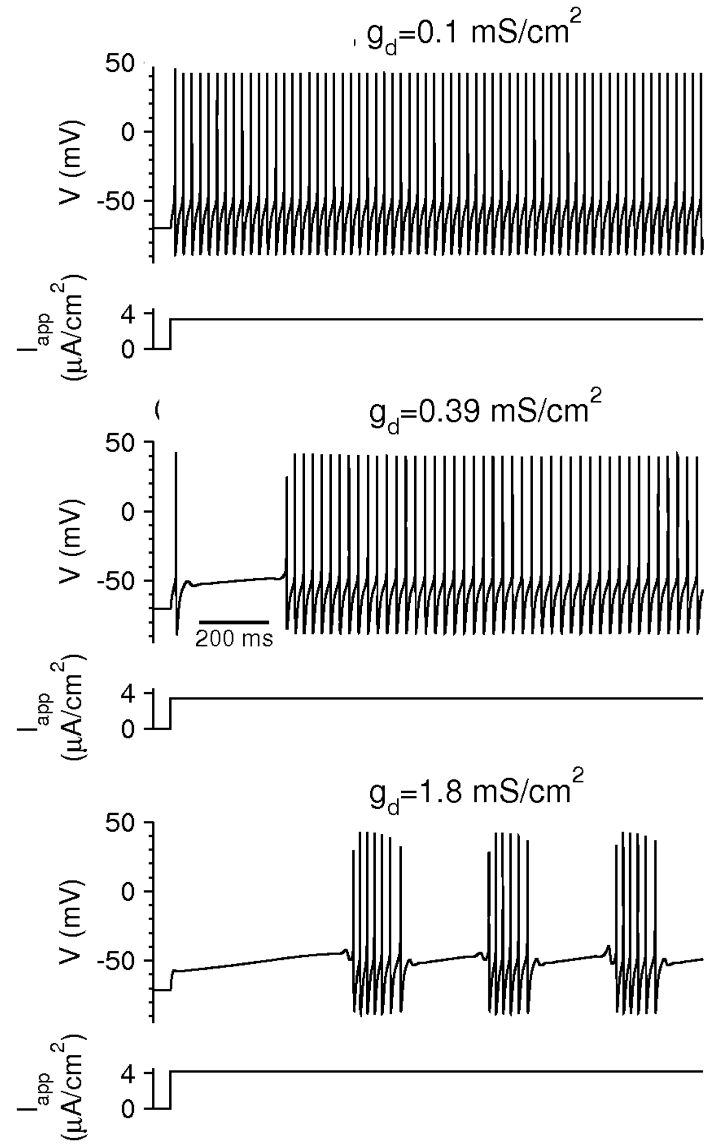


Small window current

θ_m=-24 mV

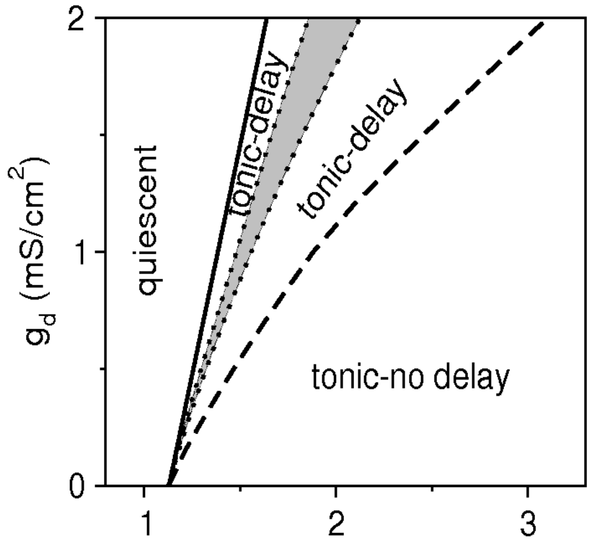


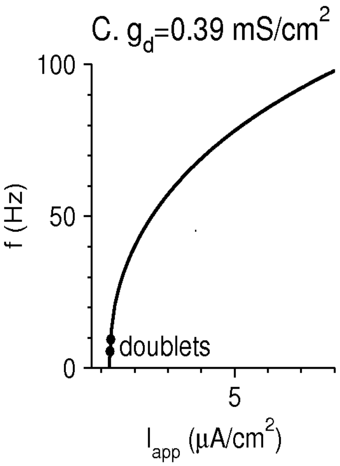


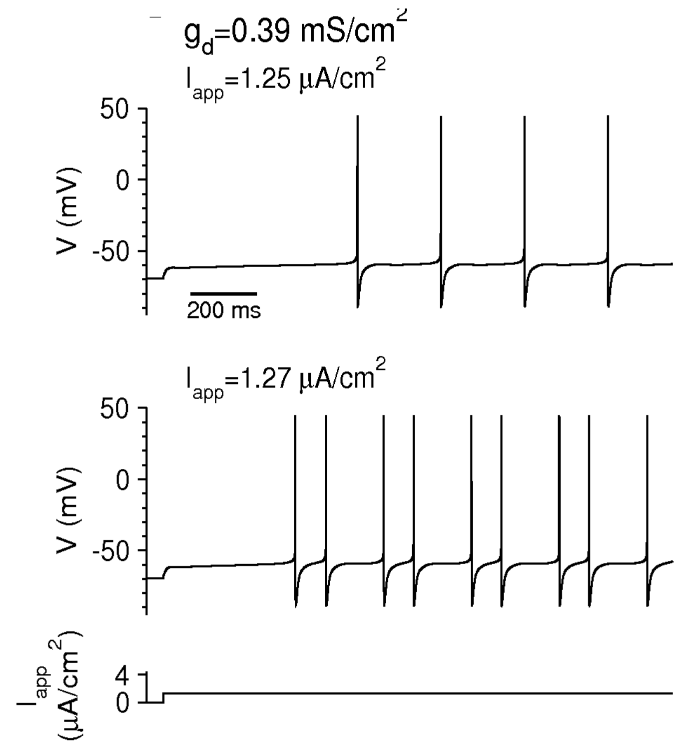


Large window current

θ_m=-28 mV

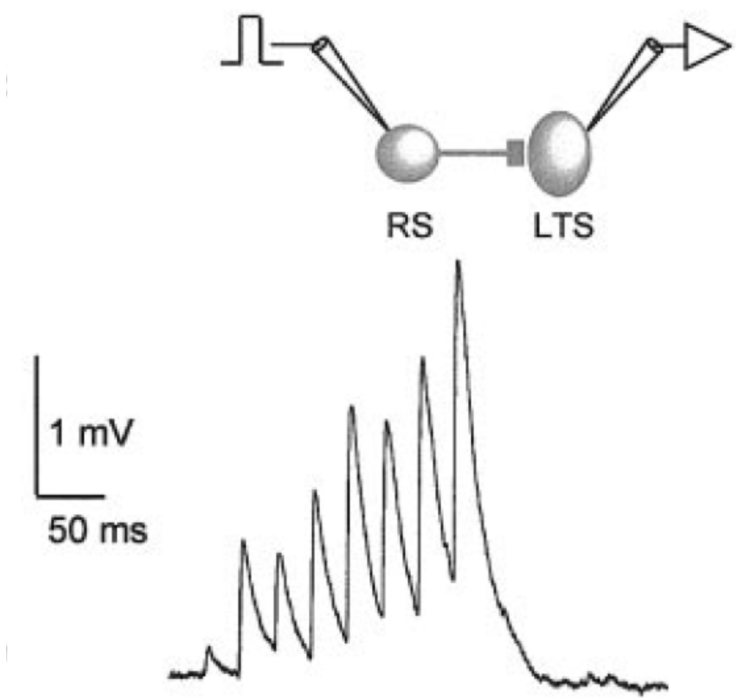






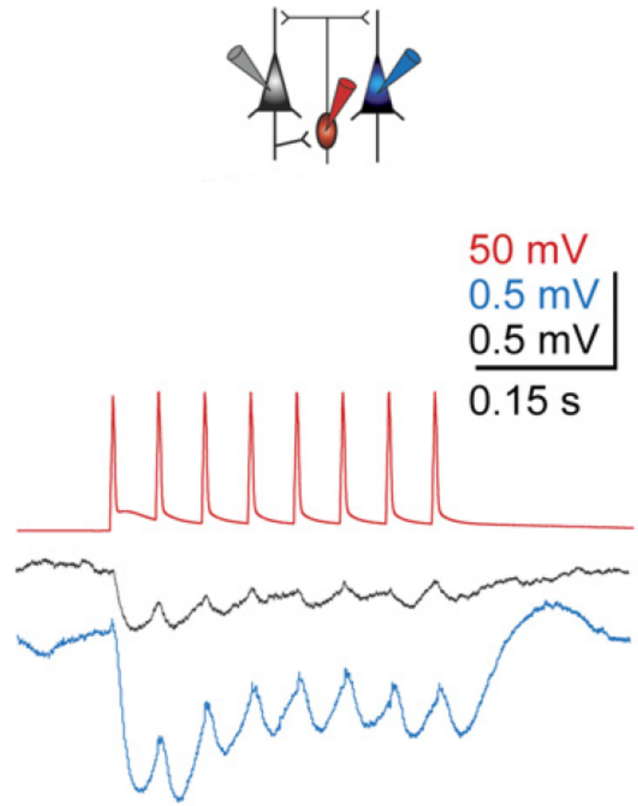
Short-term synaptic plasticity

RS-to-LTS synapses facilitate.



Beierlein, Gibson and Connors, 2003

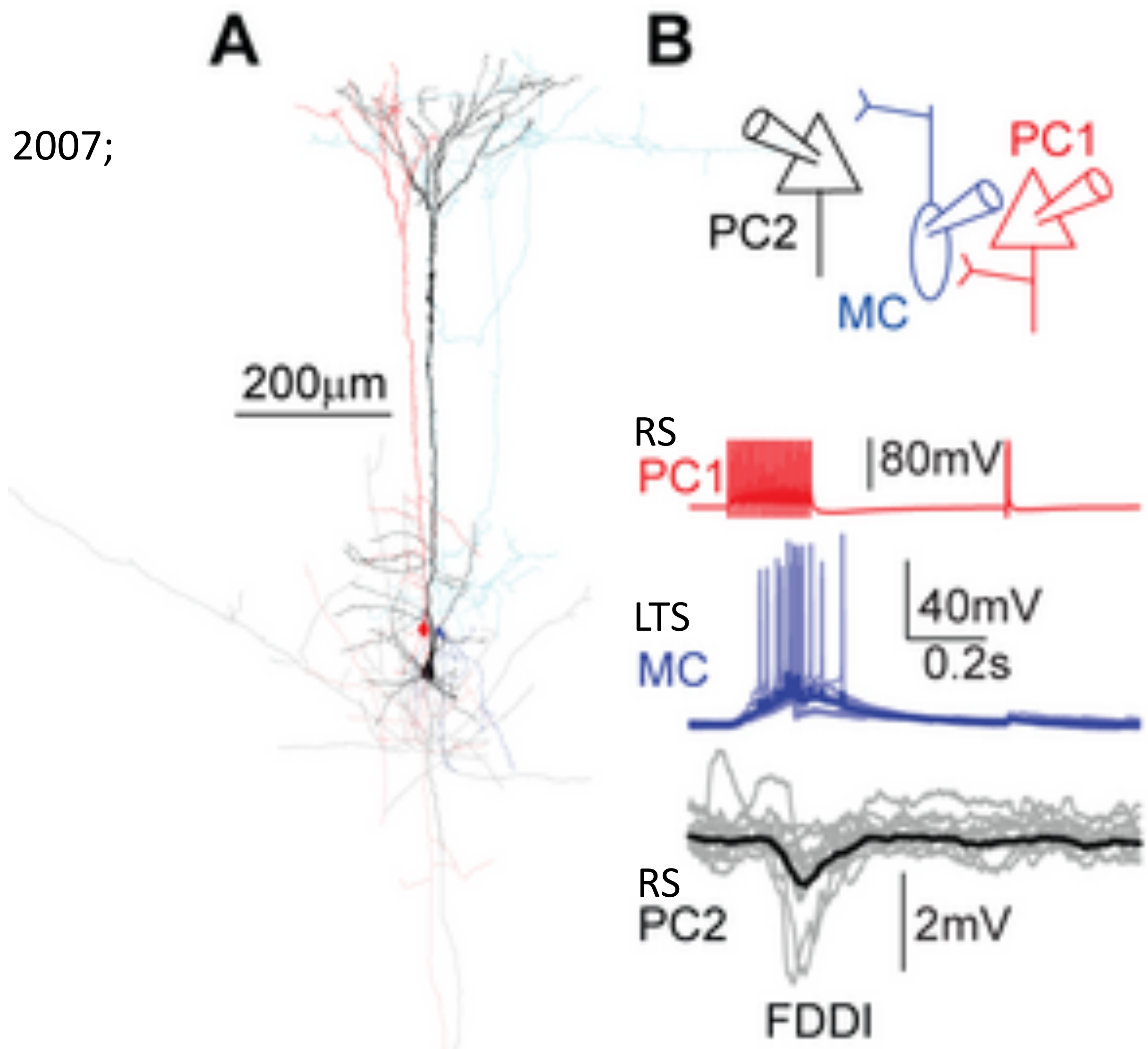
LTS-to-RS synapses depress.



Silberberg and Markram, 2007.

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.

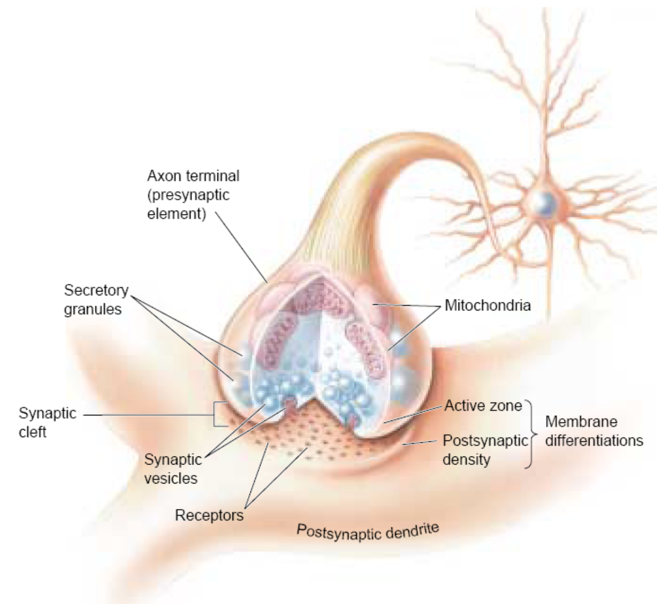
x – fraction of release sites with vesicles.

u – conditional probability of release.

Average amount of transmitter release: $T = nqxu$

Postsynaptic side:

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



Bear, Connors and Paradiso, 2007.

Depletion model of Depression: dynamics of x

Liley and North 1952, Betz 1970, Abbott, Varela, Sen and Nelson 1997, Tsodyks and Markram 1997.

"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*

Bertram, Stanley and Sherman, 1996, Bertram 1997.

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

$$D_j + Ca \underset{k_j^-}{\overset{k_j^+}{\rightleftharpoons}} B_j \qquad j = 1,2,3,4.$$

$$\sigma_j = E[B_j]$$

$$\frac{d\sigma_j}{dt} = -\left(k_j^- + k_j^+ Ca\right)\sigma_j + k_j^+ Ca \qquad j = 1,2,3,4.$$

Release probability: $\sigma_1\sigma_2\sigma_3\sigma_4$

Tsodyks-Markram model

Markram, Wang and Tsodyks, 1998.

Only one σ controls the conditional probability of release.

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

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

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

$$\sigma_1^- = 0$$

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

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

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

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

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

The rate model

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

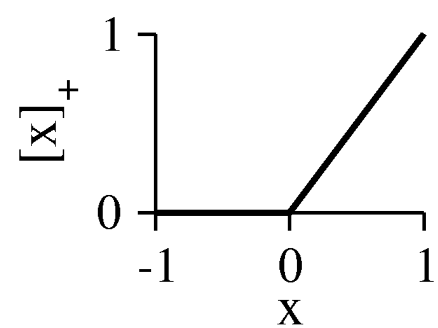
$$\frac{ds}{dt} = -\frac{s}{\tau_s} + uxM$$

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

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

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

s – synaptic activity.
M – firing rate of neuronal population.
x – fraction of vesicles available for release.
u – conditional probability of release.



Firing rates

$$M_{\mathrm{R}} = \beta_{\mathrm{R}}\left[I_{\mathrm{R}}(t) + g_{\mathrm{RR}}s_{\mathrm{RR}} - g_{\mathrm{RL}}s_{\mathrm{RL}} - g_{\mathrm{RF}}s_{\mathrm{RF}} - \theta_{\mathrm{R}}\right]_{+}$$

$$M_{\mathrm{L}} = \beta_{\mathrm{L}}\left[g_{\mathrm{LR}}s_{\mathrm{LR}} - g_{\mathrm{LF}}s_{\mathrm{LF}} - \theta_{\mathrm{L}}\right]_{+}$$

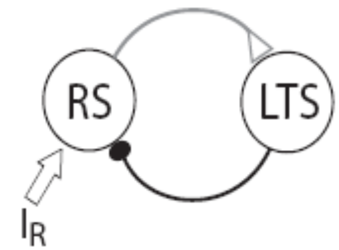
$$M_{\mathrm{F}} = \beta_{\mathrm{F}}\left[I_{\mathrm{F}}(t) + g_{\mathrm{FR}}s_{\mathrm{FR}} - g_{\mathrm{FL}}s_{\mathrm{FL}} - g_{\mathrm{FF}}s_{\mathrm{FF}} - \theta_{\mathrm{F}}\right]_{+}$$

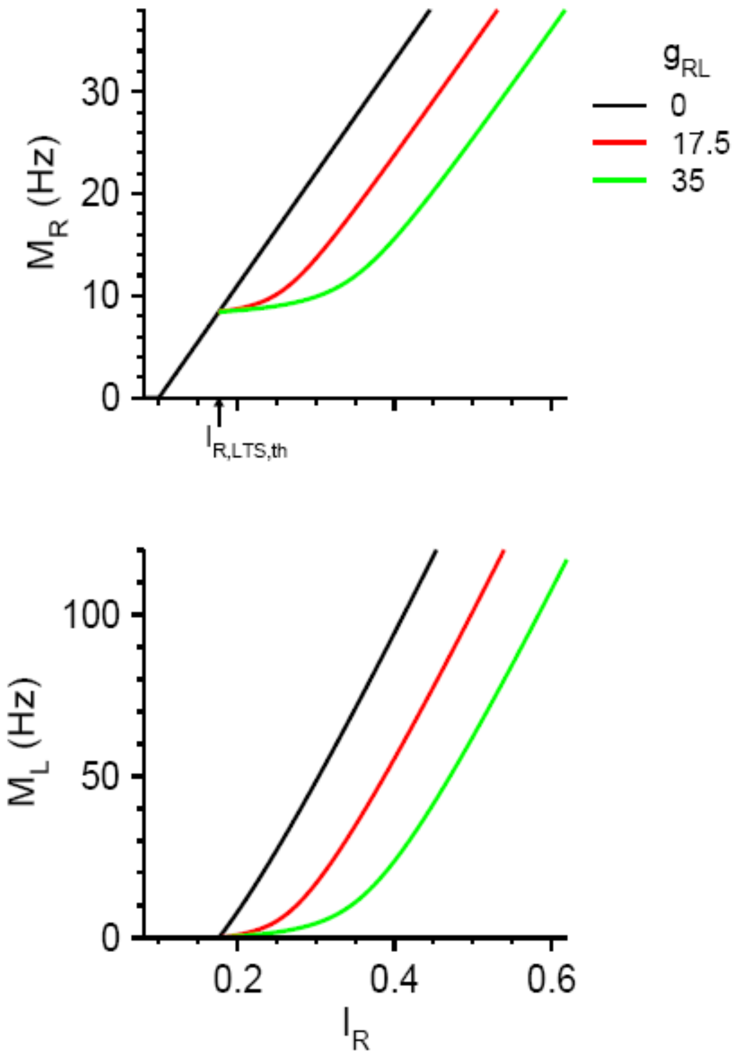
Synapse	***U***	**τ_r (ms)**	**(ms) τ_f**
RS-to-RS (RR)	0.21	463	
RS-to-LTS (LR)	0.09		670
LTS-to-RS (RL)	0.3	1250	

Wang, Markram et al., 2006.

Silberberg and Markram, 2007.

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.

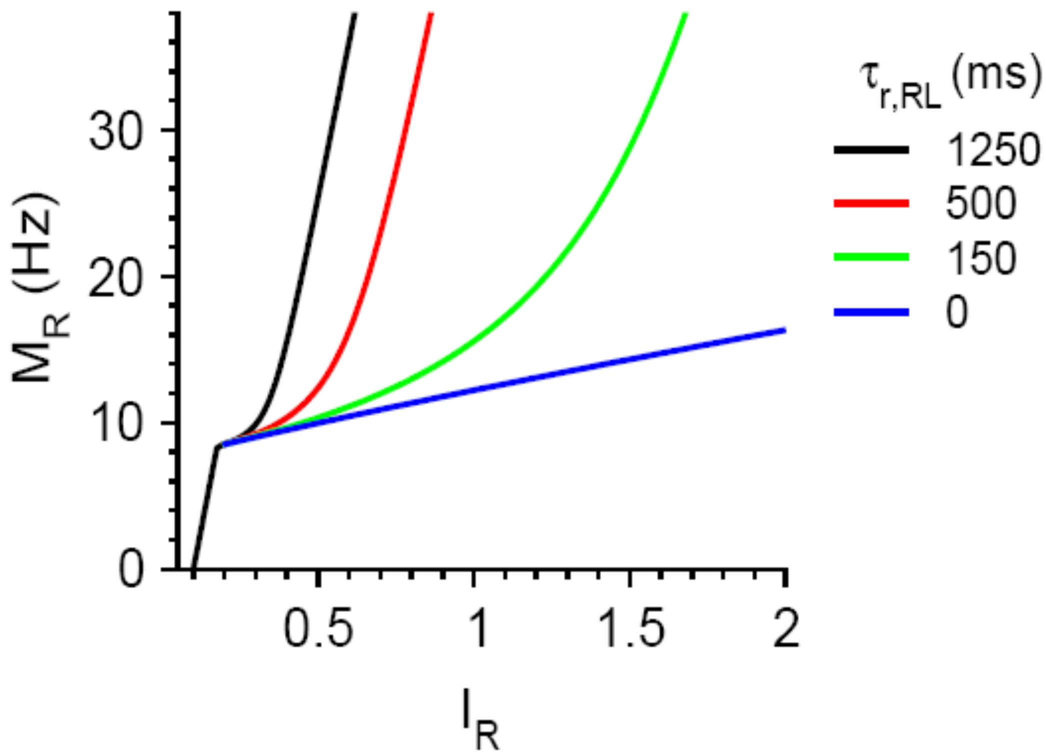
For large I_R,

$$M_R \approx \beta_R \left(I_R - \theta_R - g_{RL} \frac{\tau_{s,RL}}{\tau_{r,RL}} \right)$$

At high LTS firing rates M_{L}, the synaptic input from LTS neurons to RS neurons is constant, because

$$PSP \propto 1/M_{\mathrm{L}}$$

(Tsodyks and Markram, 1997).

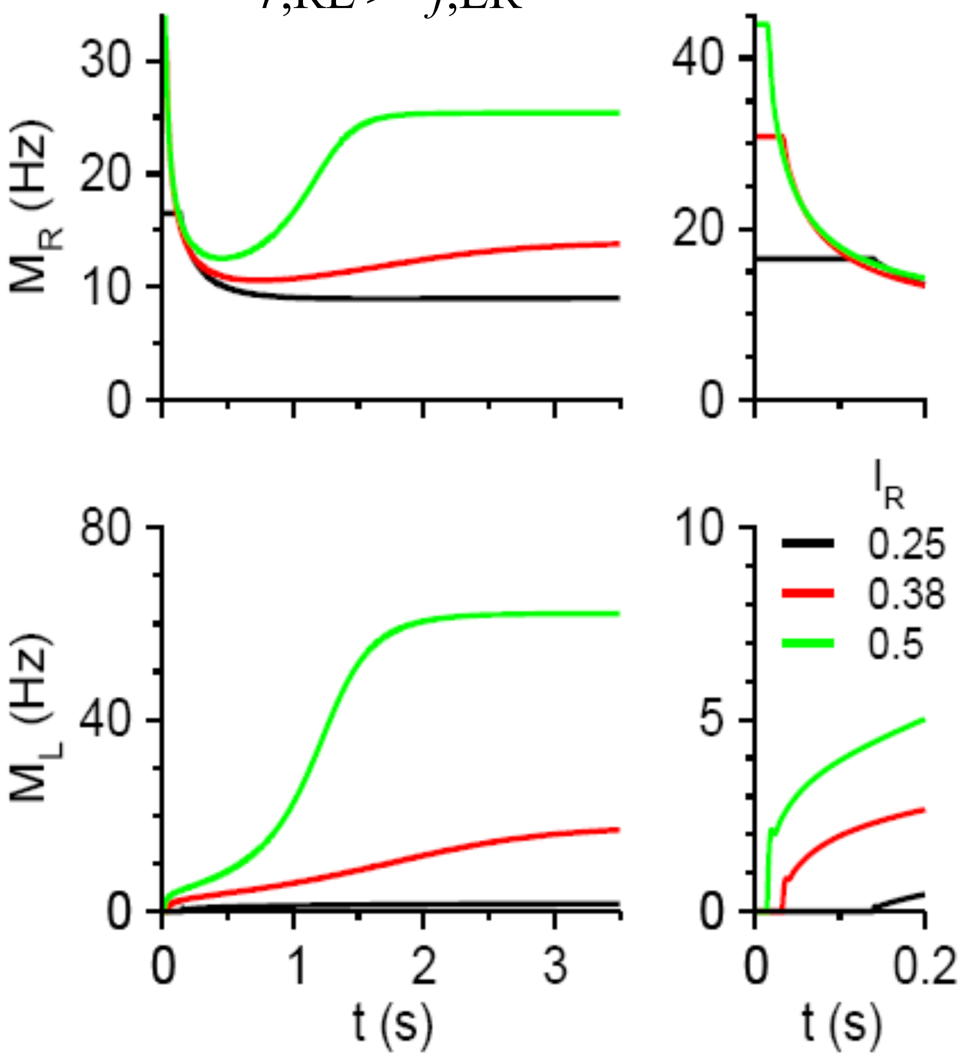


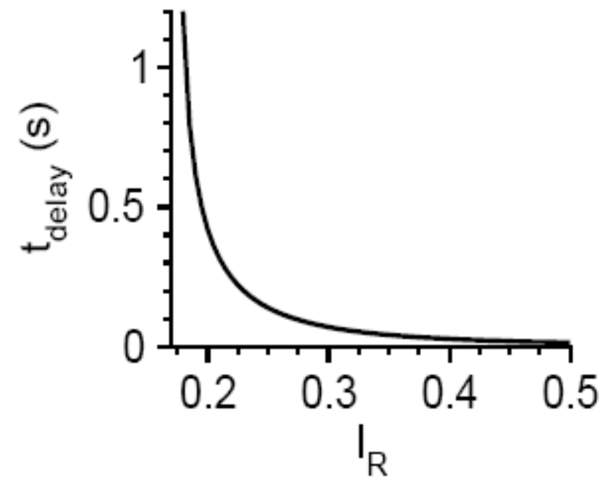
M_R (Hz)
30
20
10
0
0.5
1
1.5
2
I_R
$\tau_{r,RL}$ (ms)
1250
500
150
0

Dynamics: response to step input.

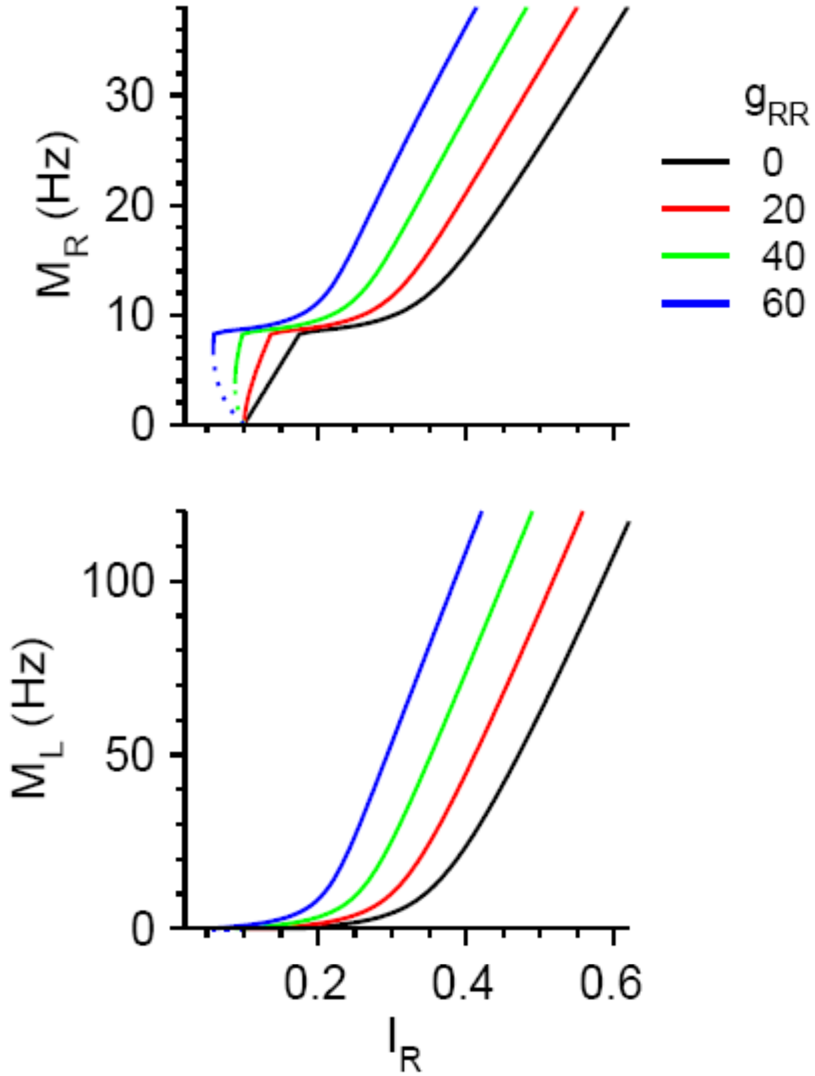
$\tau_{r,\mathrm{RL}} > \tau_{f,\mathrm{LR}}$

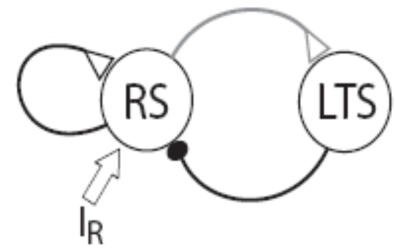
$$\tilde{I}_R(t) = I_R \Theta(t)$$





Networks with RS-to-RS synapses



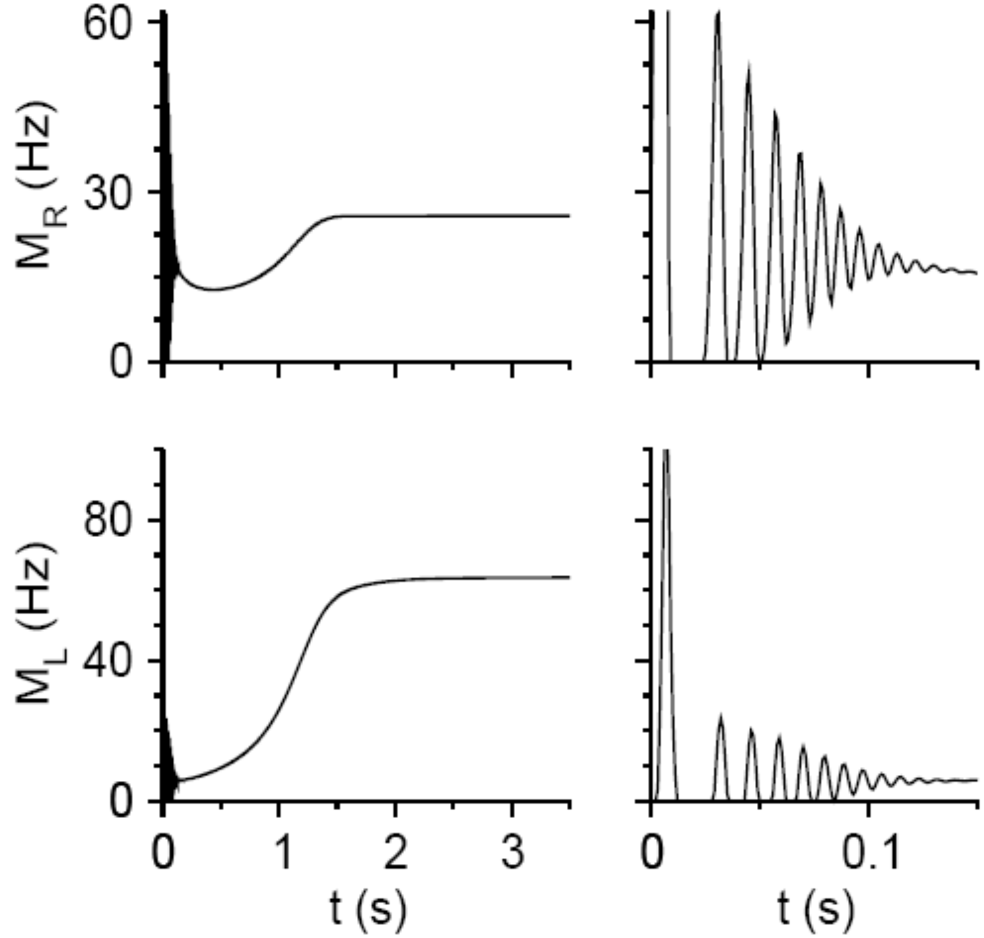


RS-to-RS synapses depress.

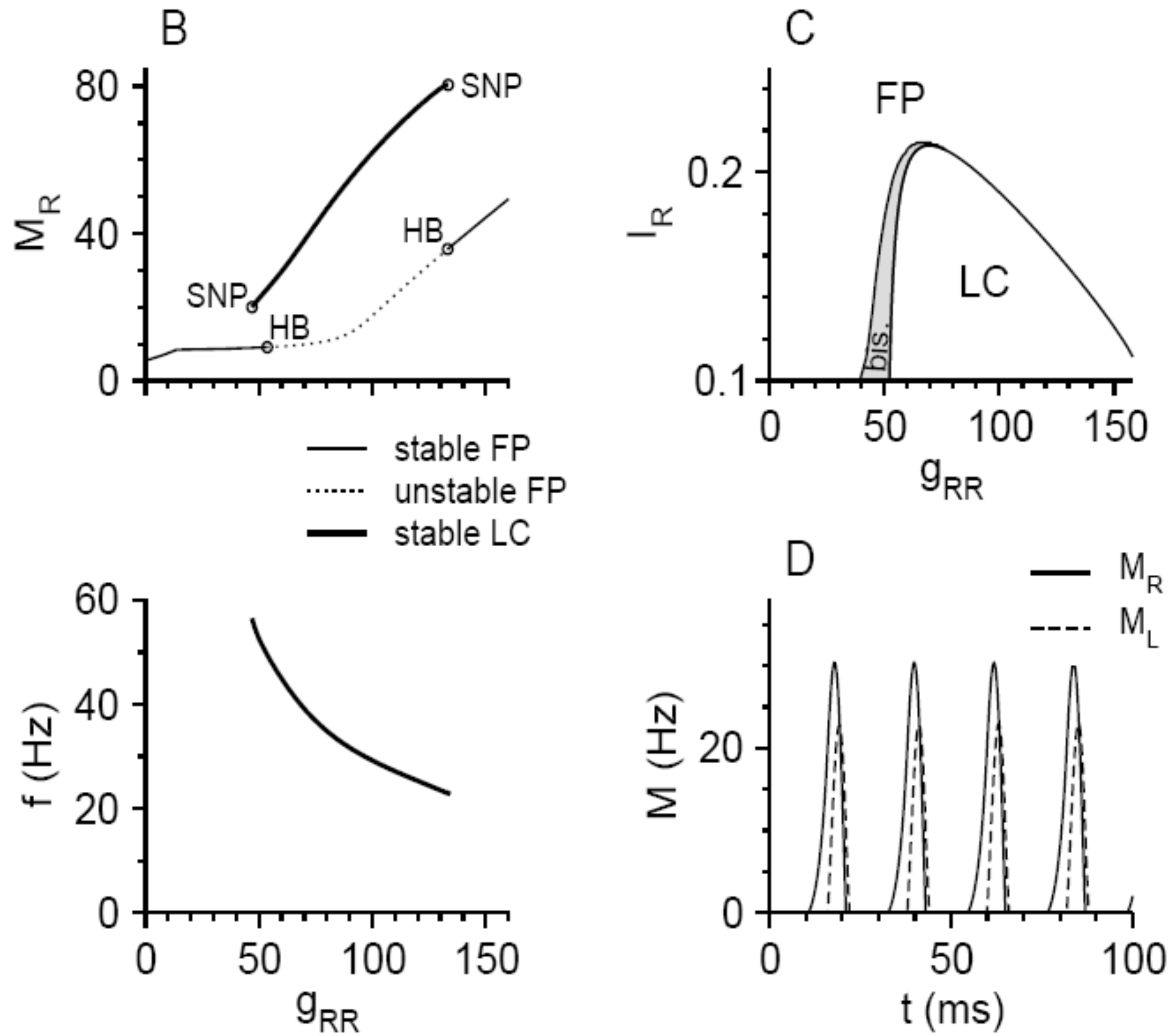
For large I_R,

$$M_R \approx \beta_R \left(I_{ext} - \theta_R - g_{RL} \frac{\tau_{s,RL}}{\tau_{r,RL}} + g_{RR} \frac{\tau_{s,RR}}{\tau_{r,RR}} \right)$$

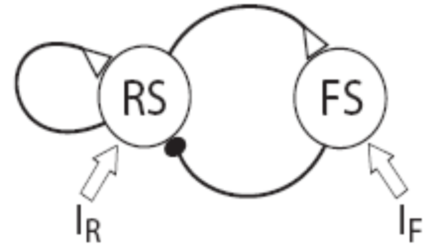
Dynamics: response to step input.

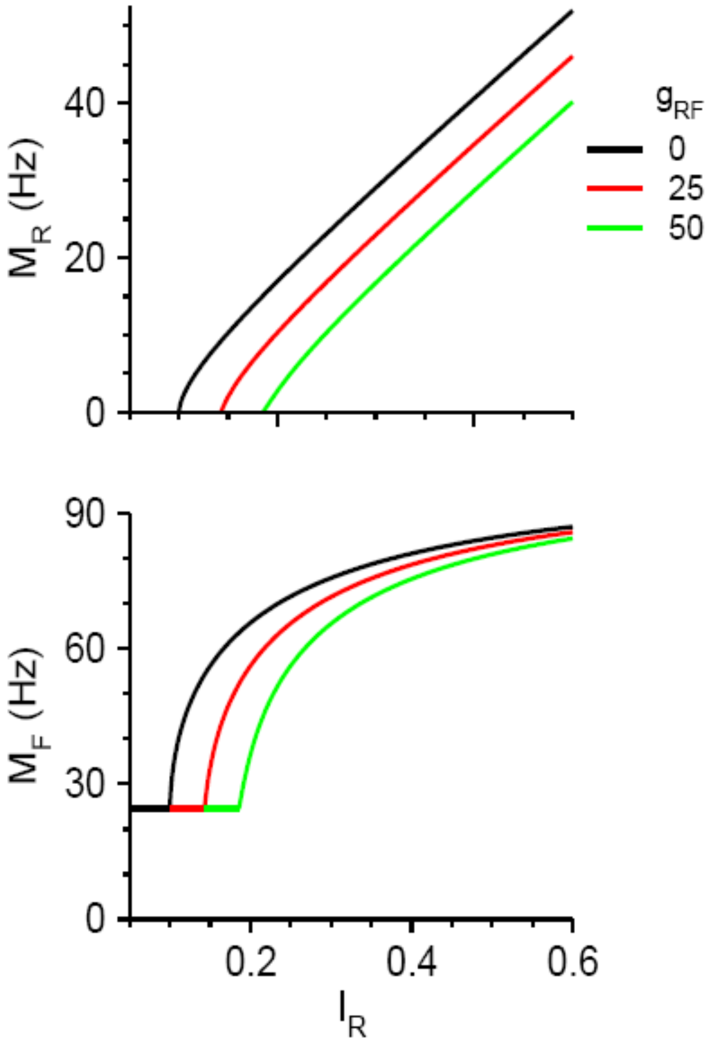


Fast oscillations



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.

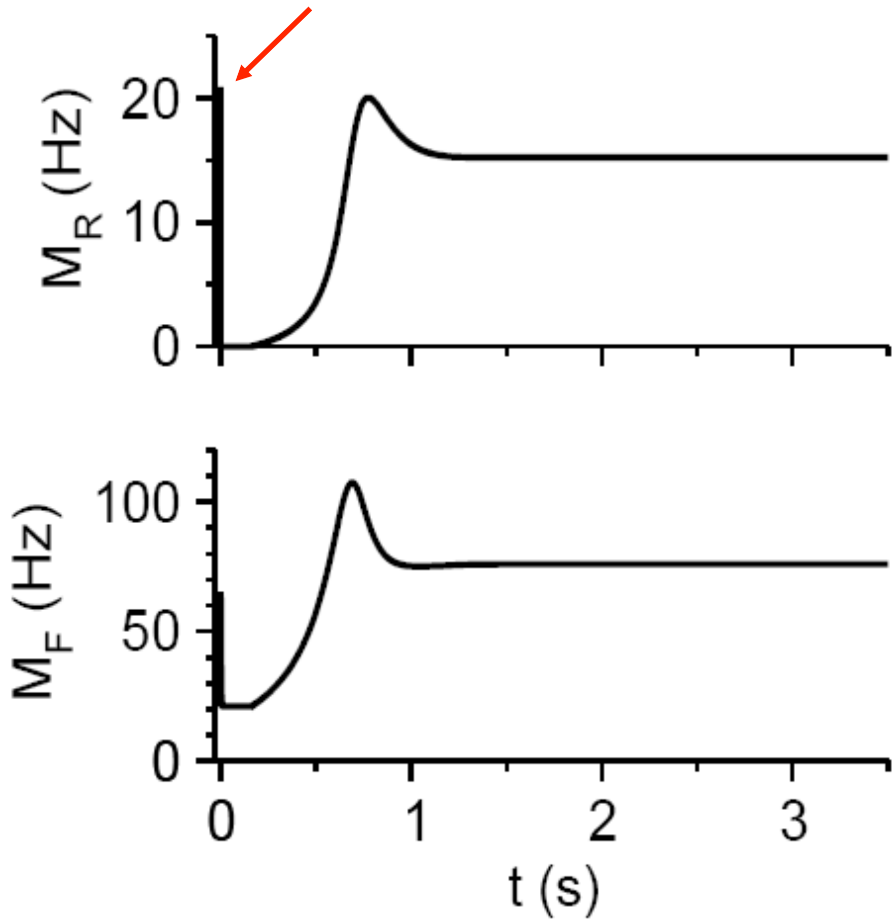
$$M_{\mathrm{F,max}} \approx \beta_{\mathrm{F}} \left(I_{\mathrm{F}} + g_{\mathrm{FR}} \tau_{s,\mathrm{FR}} / \tau_{r,\mathrm{FR}} - \theta_{\mathrm{F}} \right)$$

$$s_{\mathrm{RF,max}} = \tau_{s,\mathrm{RF}} U_{\mathrm{RF}} M_{\mathrm{F,max}} / \left(1 + \tau_{r,\mathrm{RF}} U_{\mathrm{RF}} M_{\mathrm{F,max}} \right)$$

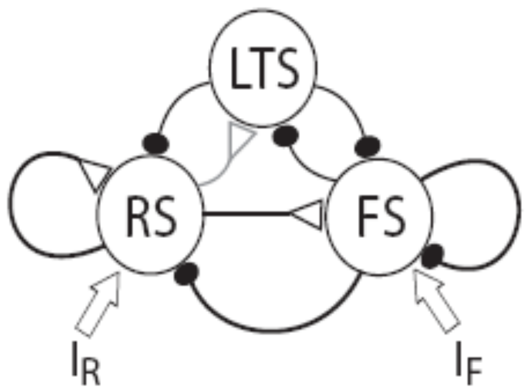
$$M_{\mathrm{R}} = \beta_{\mathrm{R}} \left(I_{\mathrm{R}} + g_{\mathrm{RR}} \tau_{s,\mathrm{RR}} / \tau_{r,\mathrm{RR}} - g_{\mathrm{RF}} s_{\mathrm{RF,max}} - \theta_{\mathrm{R}} \right)$$

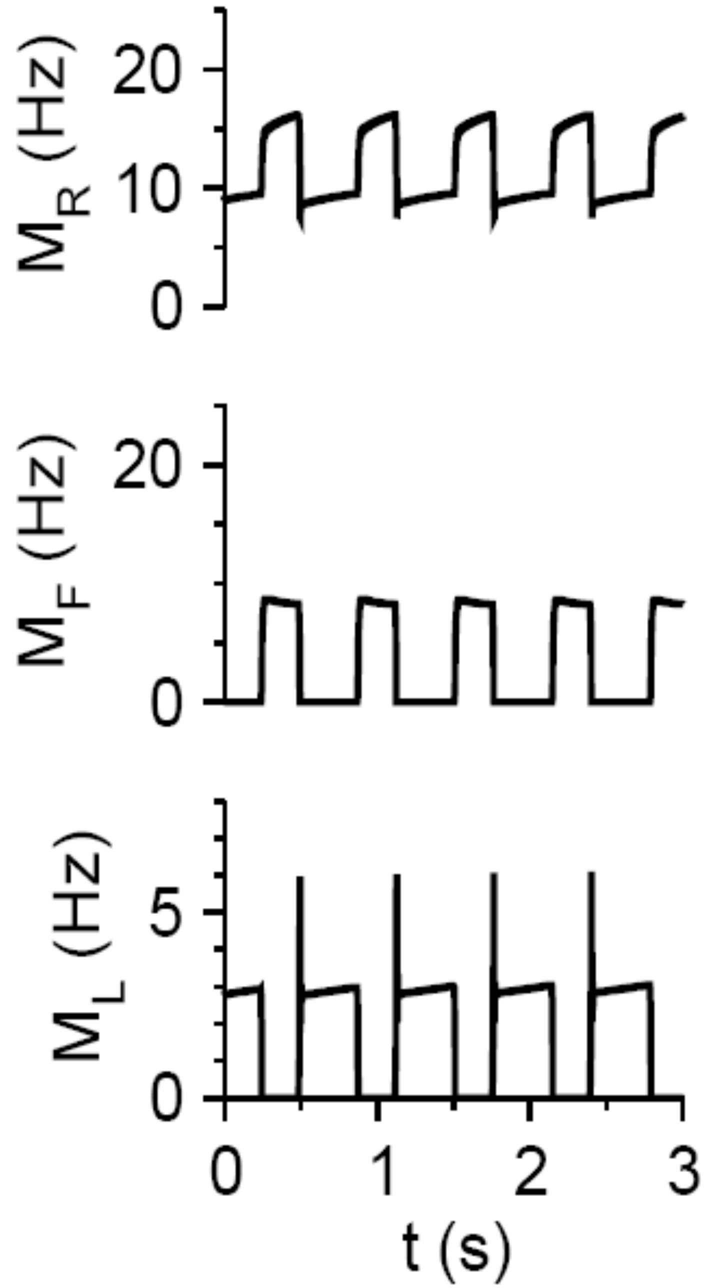
Dynamics: response to step input.

Window of opportunity (D. Simons, H. Swadlow…)



RS-LTS-FS network



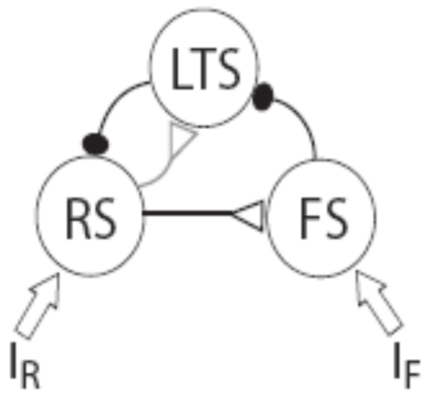


- Slow network oscillations with time scale of short-term synaptic plasticity.
- More active state: LTS neurons are silent.
- Less active state: FS neurons are silent.

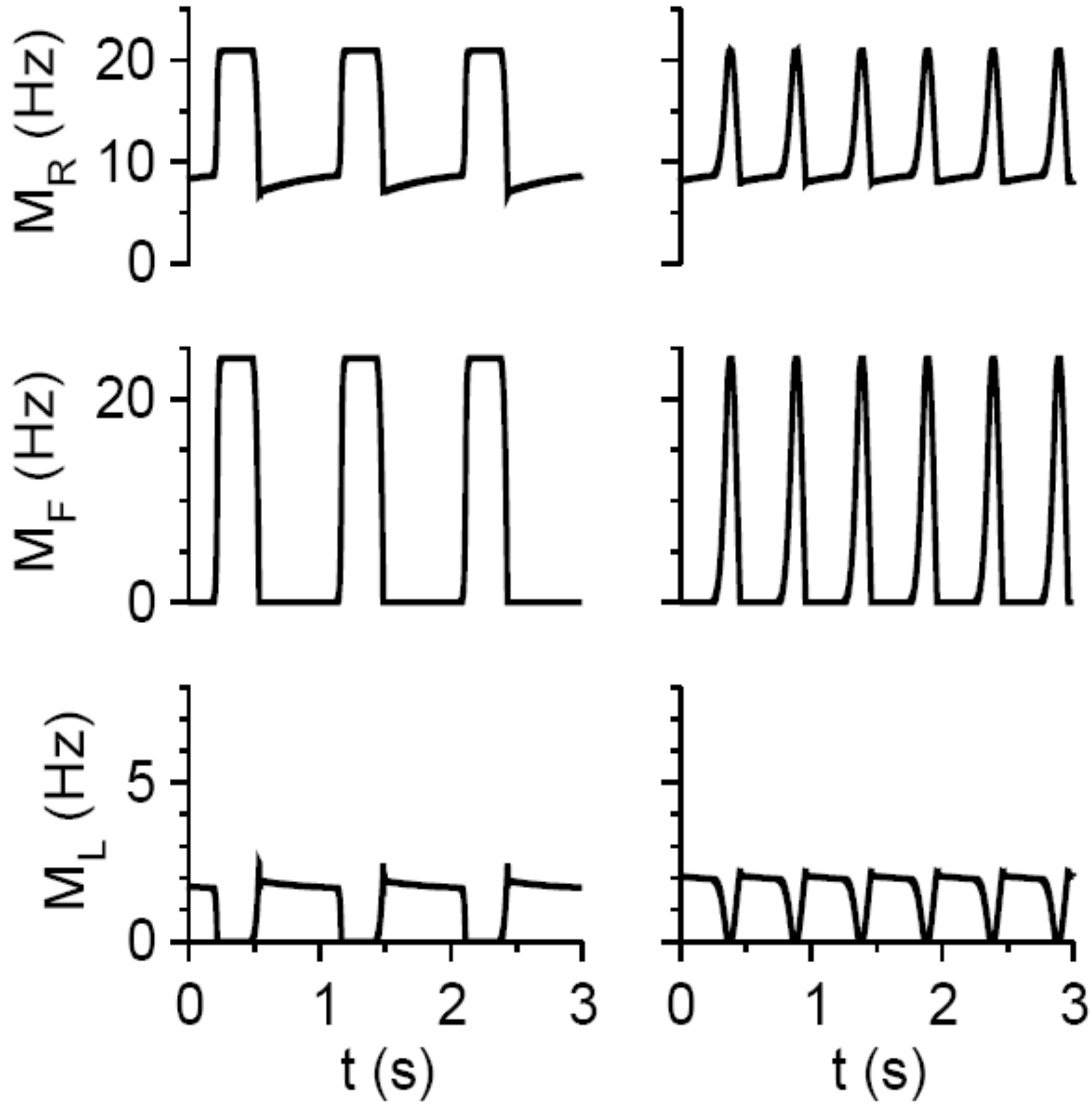
Experimental results

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

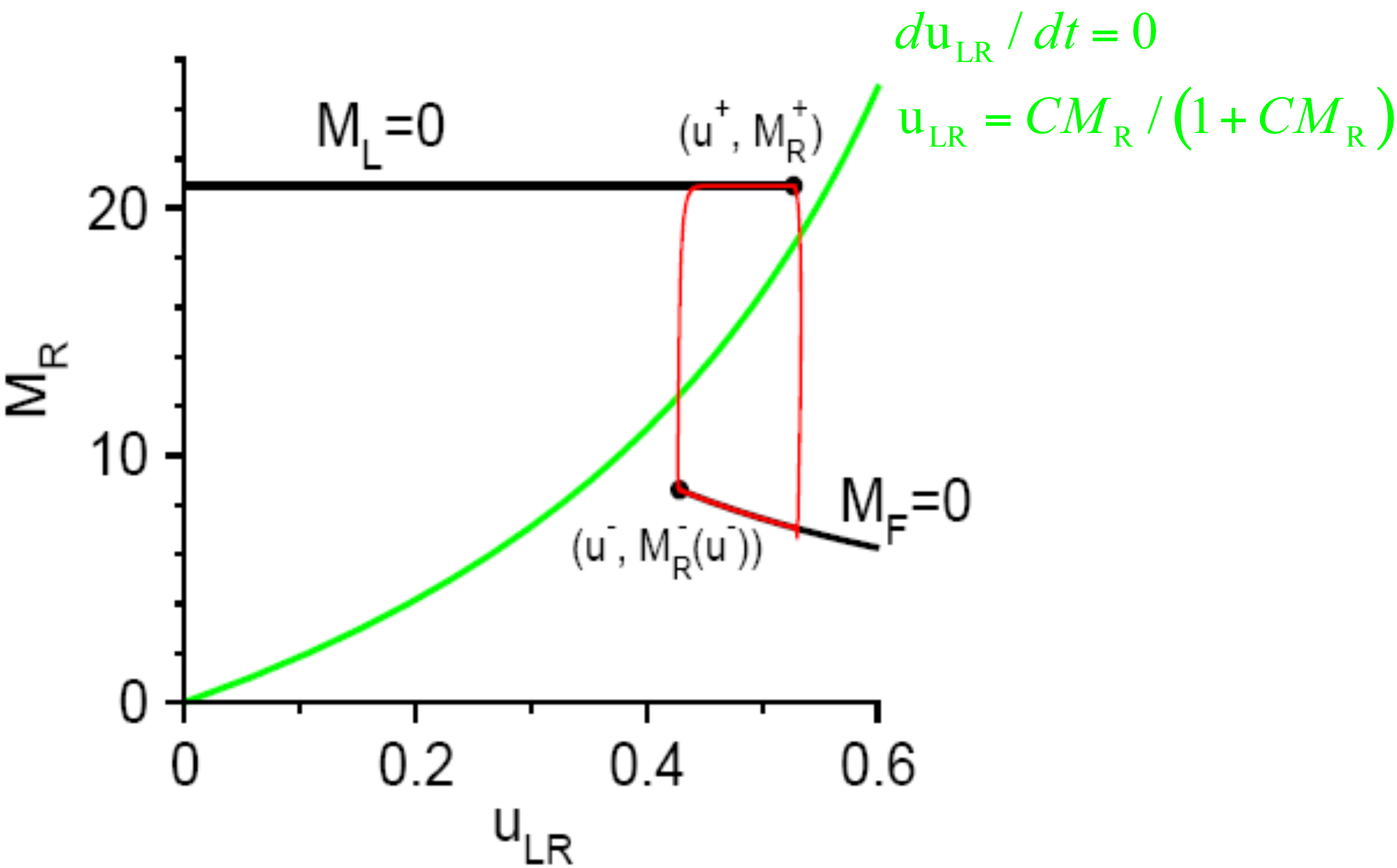
$$\frac{du_{\mathrm{LR}}}{dt} = \frac{U_{\mathrm{LR}} - u_{\mathrm{LR}}}{\tau_{f,\mathrm{LR}}} + U_{\mathrm{LR}}(1 - u_{\mathrm{LR}})M_{\mathrm{R}}$$

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

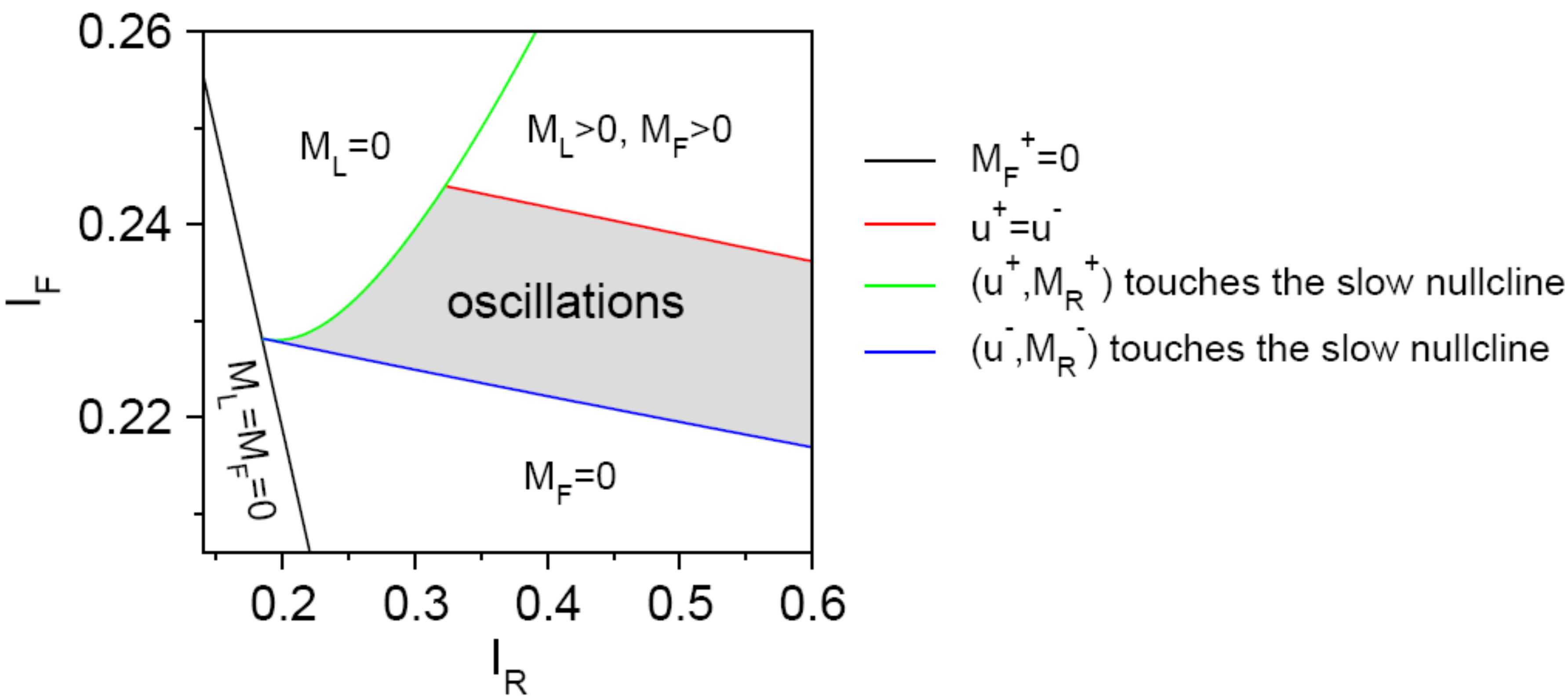
To the first order in $1/\tau_{f,\mathrm{LR}}$,

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

Fast-slow analysis



Phase diagram



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 .