In Silico Model of Neuron-Glia Interaction

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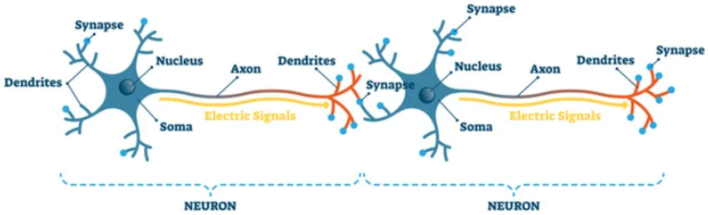
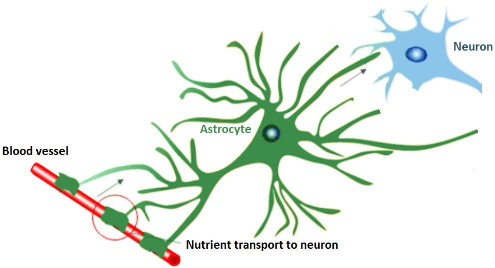
Physiological background

- Central Nervous Systems (CNS) elaborates the external stimuli from the environment to regulate and control biological processes
- Neurons are the specialized cells that accomplish these tasks through the electrical properties of the membrane
- The abrupt and rapid increase of membrane potential (spike) is transmitted from one neuron to other via Synapses



Physiological background

- The glial cells are the main cell type in the CNS. These non excitable cells appear to fall into three different types: oligodendrocytes, microglia and astrocytes
- Astrocytes perform number of biological processes such as neurons-vascular interface



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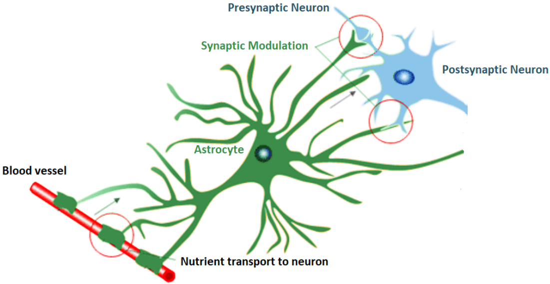

Astrocytes have a prominent role in the signalling transmission at microscopic (synaptic) scale

Physiological background

- **Tripartite Synapse**: the astrocyte is the third active element in synaptic communication between the pre- and postsynaptic neurons
- The efforts in Computation Neuroscience lead to built mathematical models to describe the interplay between astrocytes and neurons
- At mesoscopic (network) level of description, our knowledge of the effect involved neuron-glia interaction is not complete:

Current works

1. Ullah (2009): homeostatic regulation
2. Savtchenko (2014): neglect dynamical feedback between neuronal and astrocytic activity
3. Stimberg et al. (2017): Neuron-Glia network partially explored

Topic

- **Tripartite Synapse**: the astrocyte is the third active element in synaptic communication between the pre- and postsynaptic neurons
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- At mesoscopic (network) level of description, our knowledge of the effect involved neuron-glia interaction is not complete:

Purpose of present thesis

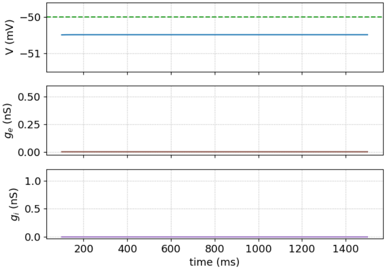
The present thesis aims to fill the gap between microscopic and mesoscopic descriptions of the interplay between neurons and astrocytes

Outline

Overview

Neuron - Conductance base Integrate and Fire

- Neural response to spikes arrival is described by subthreshold dynamics (Integrate) and spike generation mechanism (Fire)



- subthreshold dynamics:

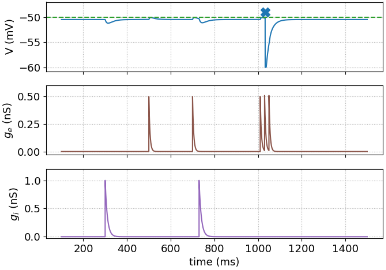
$$C_m \frac{dV}{dt} = g_l(E_l - V) + g_e(E_e - V) + g_i(E_i - V) + I_{ext}(t)$$

$$\frac{dg_e}{dt} = -\frac{g_e}{\tau_e}$$

$$\frac{dg_i}{dt} = -\frac{g_i}{\tau_i}$$

Neuron - Conductance base Integrate and Fire

- Neural response to spikes arrival is described by subthreshold dynamics (Integrate) and spike generation mechanism (Fire)



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$$C_m \frac{dV}{dt} = g_l(E_l - V) + g_e(E_e - V) + g_i(E_i - V) + I_{ext}(t)$$

$$\frac{dg_e}{dt} = -\frac{g_e}{\tau_e} \quad \text{spike arrival: } g_e \rightarrow g_e + w_e$$

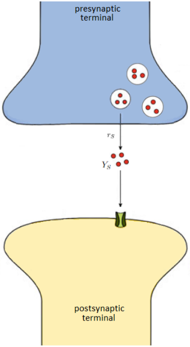
$$\frac{dg_i}{dt} = -\frac{g_i}{\tau_i} \quad \text{spike arrival: } g_i \rightarrow g_i + w_i$$

- spike generation:

1) $V(t) = V_{thr}$
2) a spike is generate (point-wise event)
3) $V(t) \rightarrow V_{res}$

Synapse - Short-Term Plasticity (STP)

- Synapses release a cert amount of neurotransmitters that induce an increase/decrease in post synaptic conductance
- STP: synaptic release r_S depends on spike timing



x_S : fraction of available resources

u_S : fraction of resources effectively released

$$\frac{du_S}{dt} = \Omega_f u_S$$

$$\frac{dx_S}{dt} = \Omega_d (1 - x_S)$$

spike arrival:

$$u_S \rightarrow u_S + u_0(1 - u_S)$$

$$r_S = x_S\, u_S$$

$$x_S \rightarrow x_S - r_S$$

Tsodyks M.V., Markram H. *Proc Natl Acad Sci* (1997)

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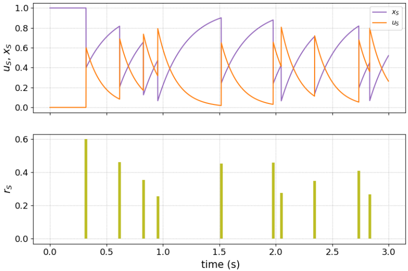

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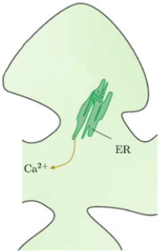
spike arrival:

$$u_S \to u_S + u_0(1 - u_S)$$
$$r_S = x_S \, u_S$$
$$x_S \to x_S - r_S$$

- r_S modulate the conductance's updating: $g_x \to g_x + r_S w_x$ with $x = e, i$

Tsodyks M.V., Markram H. *Proc Natl Acad Sci* (1997)

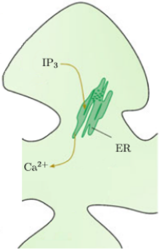
Astrocyte - G-ChI Model



- Endoplasmatic Reticulum (ER) regulates the intracellular Ca^{2+} level

De Pittà et al. *Computational Glioscience* (2019)

Astrocyte - G-ChI Model



- Endoplasmatic Reticulum (ER) regulates the intracellular Ca^{2+} level
- Inositol 1,4,5-trisphosphate (IP_3) regulates the ER calcium-release

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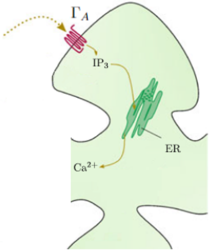
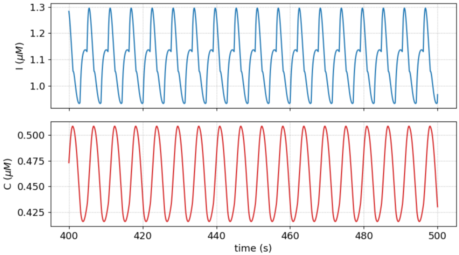


- Endoplasmatic Reticulum (ER) regulates the intracellular Ca^{2+} level
- Inositol 1,4,5-trisphosphate (IP_3) regulates the ER calcium-release
- Membrane receptors (Γ_A) regulates the intracellular IP_3 level

$$\frac{d\Gamma_A}{dt} = \text{activ.} - \text{inactiv.}$$

$$\frac{dI}{dt} = J_{in}(\Gamma_A, C, I) - J_{out}(C, I)$$

$$\frac{dC}{dt} = J_{in}(C, I) - J_{out}(C)$$



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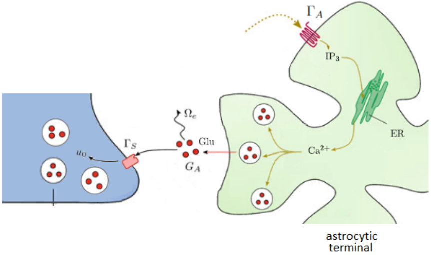
Gliomodulation of Synaptic Release



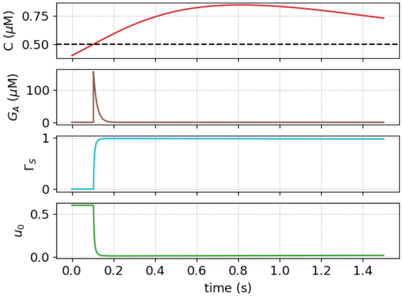
- The astrocyte releases the gliotransmitters
- The gliotrasmitters actives the presynaptic membrane receptors
- The activation/inactivation of membrane receptor modulate u_0

Gliomodulation

The astrocytic activity induced a new degrees of freedom to basal release probability

$$u_0 \equiv u_0(G_A) = u_0(\Gamma_S(G_A))$$

Release-decreasing effect



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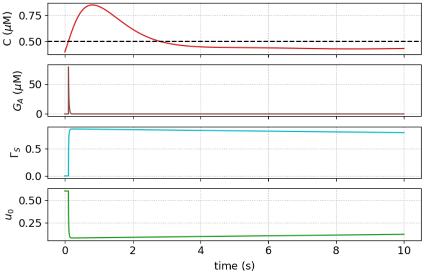
  $$u_0(t) = (1 - \Gamma_S(t))U_0^*$$

Release-decreasing effect



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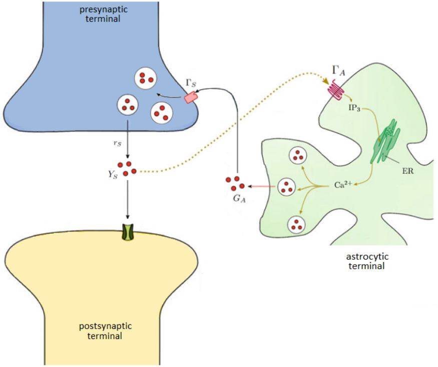
$$u_0(t) = (1 - \Gamma_S(t))U_0^*$$

Gliomodulation

The sequence of activation and inactivection of presynaptic receptors Γ_S drive the modulation of basal release probability

Overview

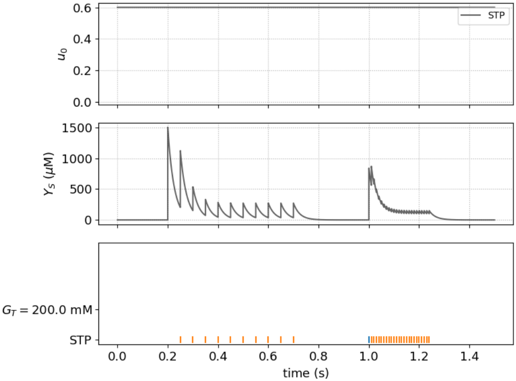
Tripartite Synapse



- Bidirectional coupling between synapse and astrocyte
- Presynaptic firing rate ν_S is the control parameter
- Modulation of basal releae probability: $u_0(t) = (1 - \Gamma_S(t))U_0^*$

From dynamical perspective, we want to point out how the presynaptic firing rate ν_S drives the dynamical behaviour

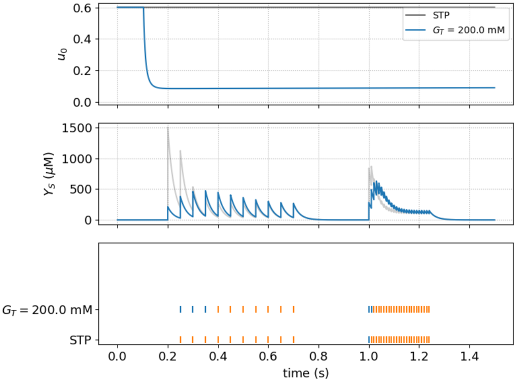
Gliomodulation effects on synaptic transmission



- STP induces depression transmission

$$\text{Pair Pulse Ratio (PPR)} = \frac{r_{S_{i+1}}}{r_{S_i}}$$

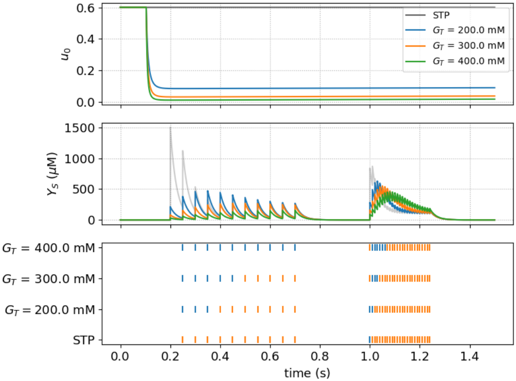
Gliomodulation effects on synaptic transmission



- STP induces depression transmission
- Gliomodulation induces facilitation transmission

Pair Pulse Ratio (PPR) $= \frac{r_{S_{i+1}}}{r_{S_i}}$

Gliomodulation effects on synaptic transmission



- STP induces depression transmission
- Gliomodulation induces facilitation transmission
- Facilitation depends on coupling strenght (G_T)

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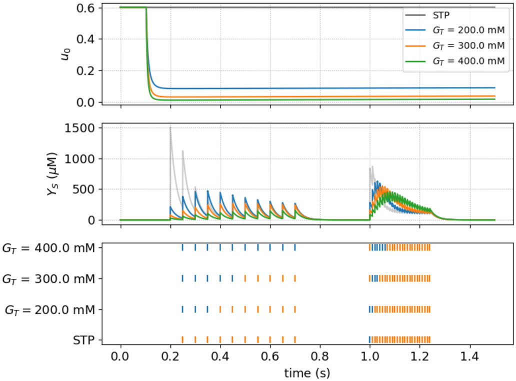
Gliomodulation effects on synaptic transmission



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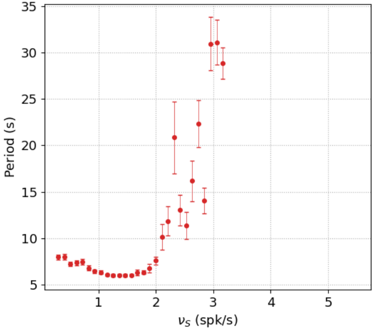
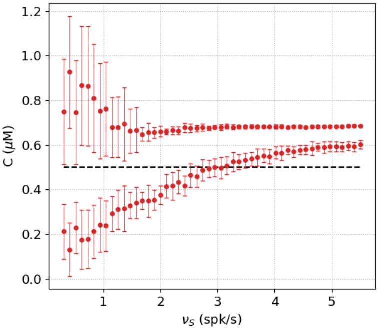
Glio-induced facilitation transmission

Astrocytic modulation leads to both depression and facilitation synaptic transmission.

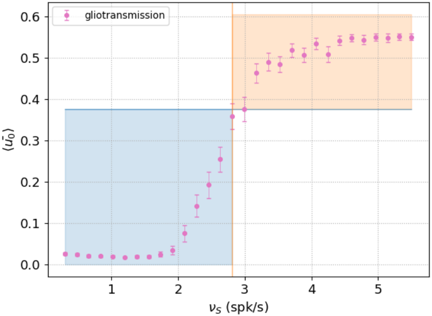
Tripartite Synapse Dynamics

- Analysis of tripartite synapses concerning the control parameter ν_S
- Presynaptic firing rate ν_S leads to astrocytic calcium oscillations across the threshold

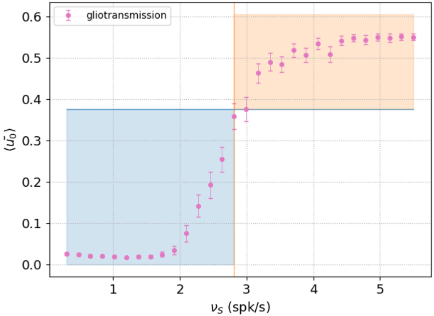


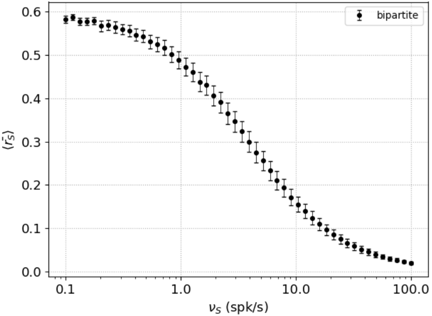


Tripartite Synapse Dynamics



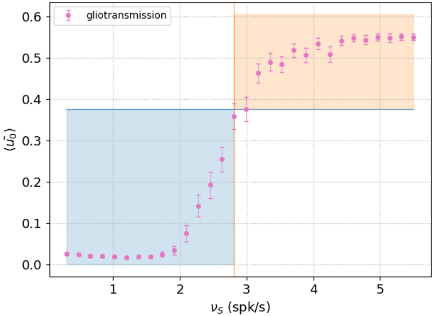
Tripartite Synapse Dynamics

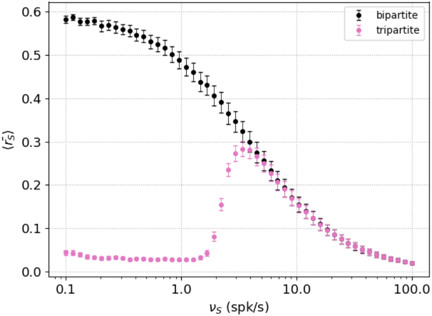




- The filtering characteristic curve of simple bipartire synapses shows monotonically decrease behaviour (low-pass filter)

Tripartite Synapse Dynamics

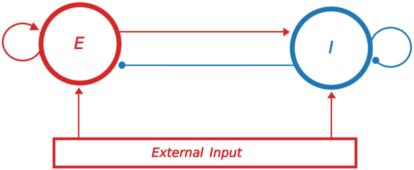




- The filtering characteristic curve of simple bipartire synapses shows monotonically decrease behaviour (low-pass filter)
- The tripartite one turns into a bell-shape curve (band-pass filter)

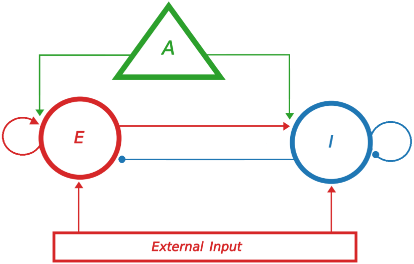
Overview

Network Scheme



- Baseline: excitatory/inhibitory neural network
- External input: Poisson spike train with $\nu_{ext}(t)$

Network Scheme



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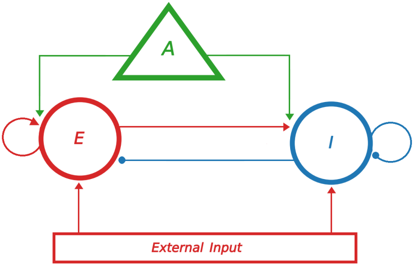
- NG network: astrocytes modulate recurent excitatory synapses

Network Scheme



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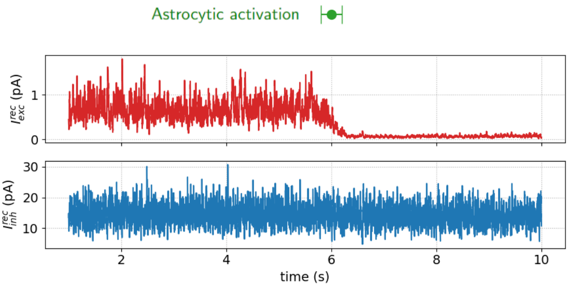
Gliomodulation at mesoscopic level of description

Compare the Neural and Neuron-Glia network dynamics through mesoscopic quantity:

$$\text{Local Field Potential (LFP)} = \sum_{l=1}^{N_e} |I_{exc_l}| + |I_{inh_l}|$$

Effect of single Gliorelease event

- Constant external input ($\nu_{ext}(t) = \nu_0$) leads to regulate recurrent excitatory current I^{rec}_{ext}

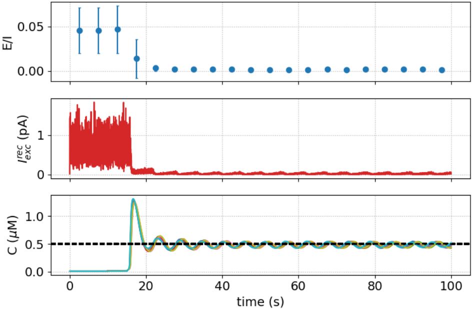


Input parameters: $\nu_0 = 7.6 \cdot 10^3$ spk/s

	LFP (a.u.)
baseline	11.4 ± 0.3
gliomodulation	11.3 ± 0.3

Long-term effect Gliotransmission

- The regulation I_{exc}^{rec} suggests a modulation of E/I balace
- Long time simulations are mandatory to observe depressing and facilitating gliomodulation effect



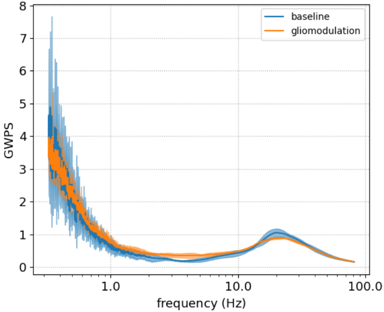
Input parameters: $\nu_0 = 7.6 \cdot 10^3$ spk/s

Modulation of E/I balance

The sequence of depressing and facilitation mechanism induced by astrocytes leads to a persistent modulation of recurrent balance

Long-term effect Gliotransmission

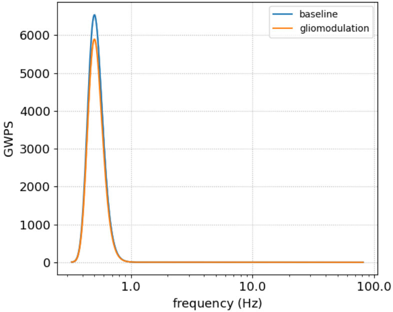
- Network oscillation are investigate through spectrum analysis of LFP
- External input: $\nu_{ext}(t) = \nu_0$



Input parameters: $\nu_0 = 7.6 \cdot 10^3 \ \mathrm{spk/s}$

Long-term effect Gliotransmission

- Network oscillation are investigate through spectrum analysis of LFP
- External input: $\nu_{ext}(t) = \nu_0 + A\sin(2\pi\omega t)$
- Modulation of frequency s: $M(s) = \frac{GWPS(s)_{\text{gliomodulation}} - GWPS(s)_{\text{baseline}}}{GWPS(s)_{\text{baseline}}}$



Gliomodulation on NG-network

Gliotransmission modulates the periodic external input: $M(0.5) = 9.6 \pm 0.6\,\%$

Input parameters: $\nu_0 = 7.6 \cdot 10^3$ spk/s; $\omega = 0.5$ Hz; $A = 0.1\,\nu_0$

Long-term effect Gliotransmission

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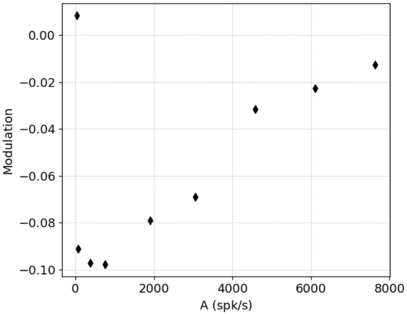

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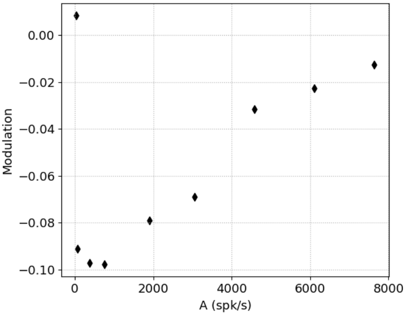


Input parameters: $\nu_0 = 7.6 \cdot 10^3$ spk/s; $\omega = 0.5$ Hz

Amplitude Gliomodulation

Amplitude modulation induced by astrocytic activity show "reverse-bell" shape behaviour

Overview

Conclusion

Original Results

Microscopic scale:

1. Derivation of Mean Field description of Tripartite Synapse
2. Gliomodulation allow the synapses to transmit the input in depression and facilitation modality
3. Characteristics curve points out the filtering of low presynaptic firing rate

Mesoscopic scale:

1. Gliomodulation filters the network oscillations but does not elicit new ones
2. Astrocytes regulate the excitatory/inhibitory recurrent balance

Conclusion

Future Perspective

- The collaboration of Scuola Superiore Sant'Anna, the Roma Sapienza University and the Camerino University aims to investigate the glioblastoma multiform (GBM)
- GBM is an aggressive brain tumour that alters the balance of inhibitory and excitatory neurotransmission and disrupts neural circuits
- Cancer cells release a huge non-physiological glutamate concentration (excitotoxicity)
- Exploiting NG-network can improve our knowledge of underpinning mechanisms of excitotoxicity and the relative alteration in neural network dynamics.

Thank you for your attention!

Neural-Glia Network

Current Model

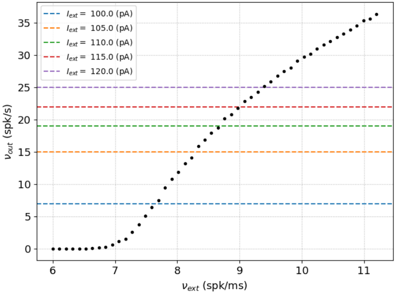
1. Homogeneous and constant external input: I_{ext}
2. Astrocytic coupling: $N_a = N_e$. The first astrocyte is coupled with all inhibitory neurons.
3. Fixed network structure and external connections
4. Time simulation $10\ \mathrm{s}$ without persistent astrocytic activity

Original Model

1. Poissonian external input $\nu_{ext}(t)$: $I_{ext} = \tilde{w}_e\,(E_e - V)$
2. Astrocytic coupling: $N_a = N_e + N_i$. Homogeneous neurons-astrocytes coupling
3. Network degrees of balance g: $g = \frac{p_e}{p_i} = \frac{w_i\,N_i}{w_e\,N_e}$
   Strength of external connection s: $\tilde{w}_e = s\,w_e$ on inhibitory neurons
4. Long-time simulation ($100\ \mathrm{s}$) with analysis of persistent activity.

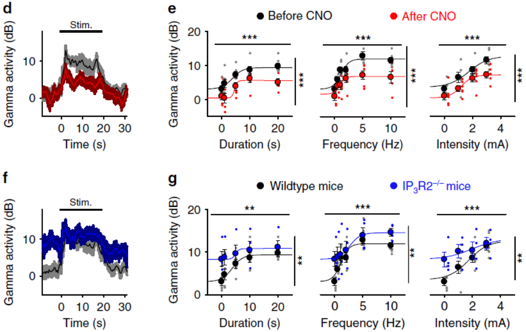
Neural-Glia Network - Poisson Input

1. evaluate the neural activity ν_{out} due to constant external current I_{ext};
2. evaluate the same activity in the case of synaptic connection with ν_{ext};
3. plot the input/output curve for different values of ν_{ext};
4. set ν_{ext} such that the activity in 1. is equal to activity in 2.



Experimental evidence

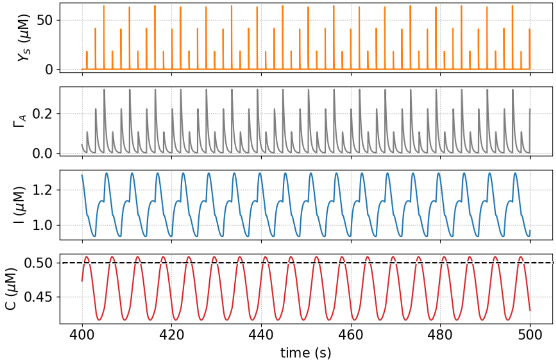
- Astrocytic population in Somatosensory Cortex (S1) mice regulate the stimulus-envoked γ-oscillation in neural network
- The astrocytic activity decrease the intensity of network oscillation in LFP recording



Lines, J., Martin, E.D., Kofuji, P. et al. *Nat Commun* (2020)

G-ChI model with homogeneous external input

- Noiseless firing rate $\nu_s = 0.5\ \mathrm{spk/s}$ dirve the dynamical behaviour
- The sequence of neurotransmitter release affect Γ_S, I and C
- The oscillation across threshold modulate the release of Y_S, onset of glio-induced facilitation transmission



Mean Field description of Bipartite Synpases

- Dynamics of mean value of variables over trial :

$$\frac{d\bar{u}_S}{dt} = \Omega_f(u_0 - \bar{u}_S) + \frac{u_0}{n_S}\sum_{l=1}^{n_S}\sum_k (1 - u_{S_l})\,\delta(t - t_{l_k})$$
$$\frac{d\bar{x}_S}{dt} = \Omega_d(1 - \bar{x}_S) - \frac{1}{n_S}\sum_{l=1}^{n_S}\sum_k u_{S_l}x_{S_l}\,\delta(t - t_{l_k})$$

- Dynamics of mean value of variables over time:

$$\frac{d\langle\bar{u}_S\rangle}{dt} = \Omega_f(u_0 - \langle\bar{u}_S\rangle) + u_0(1 - \langle\bar{u}_S\rangle)\,\nu_S(t)$$
$$\frac{d\langle\bar{x}_S\rangle}{dt} = \Omega_d(1 - \langle\bar{x}_S\rangle) - \langle\bar{u}_S\rangle\langle\bar{x}_S\rangle\,\nu_S(t)$$

Mean Field description of Bipartite Synapses

- Steady-state with constant firing rate $\nu_S(t) = \nu_S$:

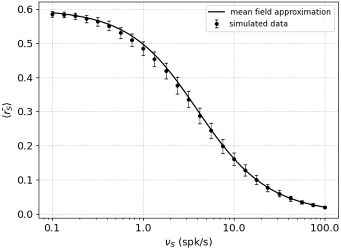
$$\langle \bar{u}_S \rangle = \frac{u_0(\Omega_f + \nu_S)}{\Omega_f + \nu_S\, u_0}$$

$$\langle \bar{x}_S \rangle = \frac{\Omega_d}{\Omega_d + \langle \bar{u}_S \rangle\, \nu_S}$$

$$\langle \bar{r}_S \rangle = \frac{u_0 \Omega_d(\Omega_f + \nu_S)}{(\Omega_f + \nu_S\, u_0)(\Omega_d + \langle \bar{u}_S \rangle\, \nu_S)}$$

- The slope of $\langle \bar{r}_S \rangle$ determine the threshold value for depression an facilitation transmission:

$$u_\theta = \frac{\Omega_d}{\Omega_d + \Omega_f}$$



Mean Filed description of Tripartite Synapse

- Mean field description starts from the average over time ($\langle\cdot\rangle$) and trials ($\bar{\cdot}$) of synaptic variables
- Assuming the statistical independence between u_0 and u_S we obtain:

$$\frac{d\langle\bar{u}_S\rangle}{dt} = \Omega_f(\langle\bar{u}_0\rangle + \langle\bar{u}_S\rangle) + \langle\bar{u}_0\rangle(1 - \langle\bar{u}_S\rangle)\,\nu_S$$

$$\frac{d\langle\bar{x}_S\rangle}{dt} = \Omega_d(1 - \langle\bar{x}_S\rangle) - \langle\bar{u}_S\rangle\langle\bar{x}_S\rangle\,\nu_S$$

$$\frac{d\langle\bar{x}_A\rangle}{dt} = \Omega_A(1 - \langle\bar{x}_A\rangle) - U_A\langle\bar{x}_A\rangle\nu_A(\nu_S)$$

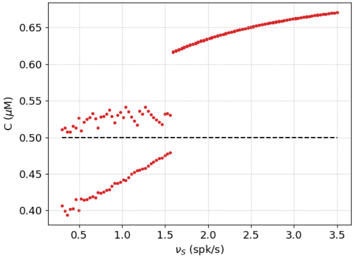
$$\frac{d\langle\bar{\Gamma}_S\rangle}{dt} = J_S U_A\langle\bar{x}_A\rangle(1 - \langle\bar{\Gamma}_S\rangle)\nu_A(\nu_S) - \Omega_G\langle\bar{\Gamma}_S\rangle$$

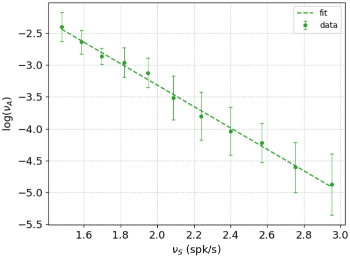
$$\langle\bar{u}_0\rangle = U_0^* + (\alpha - U_0^*)\langle\bar{\Gamma}_S\rangle$$

Mean Field desciprtion of Tripartite Synapse

- The dynamical behaviour of G-ChI model with noiseless input give insights regarding biological function $\nu_A(\nu_S)$
- Qualitative dynamical change for the bifurcation value ν_S^{bif}
- According we propose the guess fuction:

$$\nu_A = \begin{cases} \nu_A = \nu_{A_0} & \text{with } \nu_S \leq \nu_S^{bif} \\ \nu_A = \nu_{A_0} e^{-\tau_A(\nu_S - \nu_S^{bif})} & \text{with } \nu_S > \nu_S^{bif} \end{cases}$$





Mean Field desciprtion of Tripartite Synapse

- The mean field approximation well describe the shape of characteristc curve

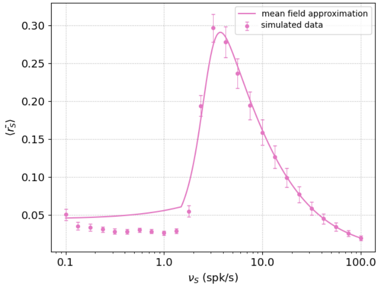
$$\langle \bar{u}_S \rangle = \frac{\langle \bar{u}_0 \rangle (\Omega_f + \nu_S)}{\Omega_f + \nu_S \langle \bar{u}_0 \rangle}$$

$$\langle \bar{x}_S \rangle = \frac{\Omega_d}{\Omega_d + \langle \bar{u}_S \rangle \nu_S}$$

$$\langle \bar{x}_A \rangle = \frac{\Omega_A}{\Omega_A + U_A \nu_A(\nu_S)}$$

$$\langle \bar{\Gamma}_S \rangle = \frac{J_S \Omega_A U_A \nu_A(\nu_S)}{\Omega_A \Omega_G + (J_S \Omega_A + \Omega_G) U_A \nu_A(\nu_S)}$$

$$\langle \bar{u}_0 \rangle = U_0^* + (\alpha - U_0^*) \langle \bar{\Gamma}_S \rangle$$



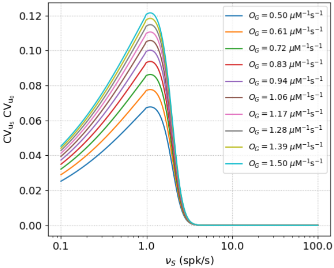
NG-network activity with external periodic signal

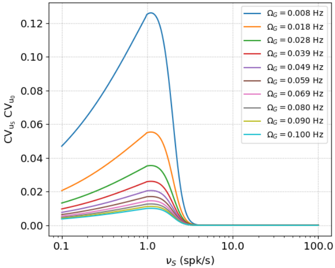
- Statistical independence between u_0 and u_S has been estimated by the Cauchy-Swarz:

$$\frac{|\langle ab\rangle - \langle a\rangle\langle b\rangle|}{\langle a\rangle\langle b\rangle} \leq \mathrm{CV}_a\,\mathrm{CV}_b$$

$$\mathrm{CV}^2_{u_S} = \frac{\Omega_f(1-\langle u_0\rangle)^2\nu_S}{(\Omega_f+\nu_s)(2\Omega_f+\langle u_0\rangle(2-\langle u_0\rangle)\nu_S}$$

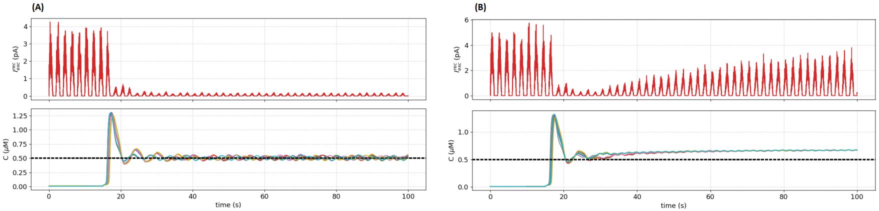
$$\mathrm{CV}^2_{u_0} = \frac{\langle\Gamma_S\rangle^2}{(1-\langle\Gamma_S\rangle)^2}\,\frac{\Omega_G^2}{({}_G+(1-\beta)\nu_A)(\Omega_G+(1+\beta)\nu_A)}$$





NG-network activity with external periodic signal

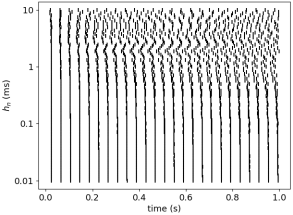
- The persistent astrocytic activity depends on Amplitude of external periodic input
- Intense amplitude does not further sustain gliotransmission. The amplitude gliomodulation tends to 0.

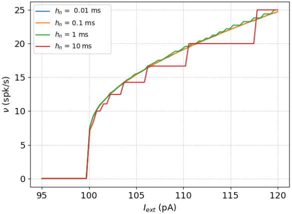


External Input: $\nu_{ext}(t) = \nu_0 + A \sin(2\pi\omega t)$. Parameters: $\omega = 0.5$ Hz; $\nu_0 = 7.6 \cdot 10^3$ spk/s; A) $A = 0.4\,\nu_0$; b) $A = 0.6\,\nu_0$

Numerical Integration

- IF generates different firing rate concerning the integration step h_n





- NG-network dynamics in the neighborhood of $h_n = 0.05\ \mathrm{ms}$