

# 1 Tripartite Synapses

The concept of tripartite synapses is used to describe the close structural and functional association between astrocytes and synaptic partners. Therefore, a tripartite synapses encompasses the impact of astrocytes on the extracellular space surrounding synapses, modulating synapses formation as well as synaptic function via uptake of neurotransmitters and delivery of acting signaling molecules.

Indeed, intracellular  $\text{Ca}^{2+}$  elevations, either induced by spontaneous astrocytic activity or evoked by neuronal firing, can trigger the release of different active substances from astrocytes, the so-called gliotransmitters. These gliotransmitters, include glutamate, can modulate and control neuronal activity in a huge different way, both through activation of pre- and postsynaptic receptors.

Here the focus is the description of presynaptic pathway regulation of glutamate released from astrocyte, described by the following approach: (i) synaptic release model and related neurotransmitter time course in the extracellular space (ECS), (ii) astrocytic  $\text{Ca}^{2+}$ -dependent gliotransmitter model and gliotransmitter dynamics in ECS and (iii) the modulation of synaptic release by the presence of astrocytic exocytosis.

## Synaptic Model

The TM model describes synaptic release ( $r_S$ ) by the product of two factors: (i) the probability of neurotransmitter-containing vesicles to be available for release ( $x_S$ ), and (ii) the probability of such vesicles to be effectively released by an AP ( $u_S$ ), which correlates with intrasynaptic  $\text{Ca}^{2+}$  levels and the ensuing state of occupancy (activation) of the  $\text{Ca}^{2+}$  sensory of synaptic neurotransmitter exocytosis. The time evolution equations for  $u_S(t)$  and  $x_S(t)$  reads

$$\begin{aligned}\frac{du_S}{dt} &= -\Omega_f u_S + u_0 \sum_k (1 - u_S^-) \delta(t - t_k) \\ \frac{dx_S}{dt} &= \Omega_d (1 - x_S) - \sum_k u_S^+ x_S^- \delta(t - t_k) \\ r_S(t_k) &= u_S^+ x_S^- = u_S(t_k^+) x_S(t_k^-)\end{aligned}\tag{1}$$

where the delta function denotes an action potential arriving at time  $t_k$ ,  $u_S^+$  and  $x_S^-$  are respectively the value of  $u_S$  immediately after a generic spikes and the value of  $x_S$  immediately before a generic spikes. Assuming a total vesicular glutamate concentration of  $Y_T$ , the released glutamate, expressed as concentration in the synaptic cleft, is then equal to  $Y_{rel}(t_k) = \rho_c Y_T r_S(t_k)$ , where  $\rho_c$  represents the ratio between vesicular and synaptic cleft volumes. The time course of synaptically released glutamate in the cleft ( $Y_S$ ) depends on several mechanisms, including clearance by diffusion, uptake, and/or degradation. In the simplest approximation, the contribution of these mechanisms to glutamate time course in the cleft may be modeled by a first-order degradation reaction of characteristic time so that:

$$\frac{dY_S}{dt} = -\Omega_c Y_S + \sum_k Y_{rel} \delta(t - t_k)\tag{2}$$

To complete this description the dynamics of presynaptic receptors must be taken into account. The pool of presynaptic receptors target by gliotransmitters is composed by a fraction  $\Gamma_S$  of gliotransmitter-bounded receptors and a complementary  $1 - \Gamma_S$  of available (not bounded) receptor, so that  $\Gamma_S$  evolves according to:

$$\frac{d\Gamma_S}{dt} = O_G G_A (1 - \Gamma_S) - \Omega_G \Gamma_S\tag{3}$$

## Gliotransmitter exocytosis

Astrocytic glutamate exocytosis is modeled akin to synaptic glutamate release, assuming that a fraction  $x_A(t)$  of gliotransmitter resources is available for release at any time. Then, every time  $t_j$  that astrocytic  $\text{Ca}^{2+}$  increases beyond a threshold concentration  $C_\theta$ , a fraction of readily releasable astrocytic glutamate resources, that is,  $r_A(t_j) = U_A x_A(t_j^-)$ , is released into the ECS and later reintegrated at rate  $\Omega_A$ . Hence  $x_A$  evolves according to:

$$\frac{dx_A}{dt} = \Omega_A(1 - x_A) - \sum_j r_A \delta(t - t_j) \quad (4)$$

Similarly to synaptic case, it is possible to estimate the contribution to glutamate concentration in the ECS space ( $G_A$ ), resulting from a quantal glutamate release event by the astrocyte at  $t = t_j$ , as  $G_{rel}(t_j) = \rho_e G_T r_A(t_j)$ , where  $G_T$  represents the total vesicular glutamate concentration in the astrocyte and  $\rho_e$  is the volume ratio between glutamate-containing astrocytic vesicles and periastrorcytic space. Then, assuming a clearance rate of glutamate of  $\Omega_e$ , the time course of astrocyte-derived glutamate in the ECS comprised between the astrocyte and the surrounding synaptic terminals is given by:

$$\frac{dG_A}{dt} = -\Omega_e G_A + \sum_j G_{rel} \delta(t - t_j) \quad (5)$$

### Modulation of Synaptic Release by Gliotransmitter

The gliotransmitter modulation of synaptic release can be reproduced by the TM synaptic model, making the variable  $u_S$  in (1) depend on gliotransmitter dynamics in the ECS, i.e.  $G_A$  in equation (5).

It may be assumed that basal synaptic release probability  $u_0$  is not constant, but rather it is a function of  $G_A$  through the fraction  $\Gamma_S$  of presynaptic receptor that are activated by released gliotransmitter molecules

$$u_0 \equiv u_0(G_A) = u_0(\Gamma_S(G_A)) \quad (6)$$

In the absence of quantitative physiological data, the function  $u_0(\Gamma_S)$  can be taken analytic around zero that its first-order expansion is considered accordingly:

$$u_0(\Gamma_S) \simeq u_0(0) + u'_0(0)\Gamma_S + O(\Gamma_S^2) \quad (7)$$

The zeroth-order term  $u_0(0) = \text{const} = U_0^*$  corresponds to the value of  $u_0$  in the absence of astrocyte: that is the zeroth-order approximation falls back to the classic TM model (1). To express  $u'_0(0)$  instead, it may be noted that both  $u_0(\Gamma_S)$  and  $\Gamma_S$  are defined in the interval  $[0, 1]$ , so that  $u_0(\Gamma_S)$  must either increase or decrease with  $\Gamma_S$  depending on whether gliotransmission stimulates or inhibits synaptic release. In the simplest scenario, the choice of  $u'_0 = \alpha - U_0^*$  can be made so that, neglecting the terms of  $O(\Gamma_S^2)$  in equations (7) ultimately provides

$$u_0(\Gamma_S) = U_0^* + (\alpha - U_0^*)\Gamma_S \quad (8)$$

The parameter  $\alpha$  in the above equation lumps in a phenomenological way information on the effect of gliotransmission on synaptic release. For  $0 \leq \alpha < U_0^*$ ,  $u_0$  decreases with  $\Gamma_S$ , consistently with the *release-decreasing* effect of gliotransmission on synaptic release. This could be the case of astrocytic glutamate targeting presynaptic kainate receptors or group II/III metabotropic receptors. For  $U_0^* < \alpha \leq 1$ ,  $u_0$  increases with  $\Gamma_S$ , consistent with a *release-increasing* effect of gliotransmission on synaptic release, like in the case of glutamate in association with presynaptic NMDA receptors or group I metabotropic receptors. Finally, for  $\alpha = U_0^*$ , it is  $u_0 = U_0^*$ , independently of  $\Gamma_S$ . This case corresponds to *occlusion*, that is no net effect of gliotransmission on synaptic release due to the simultaneous activation of stimulatory and inhibitory receptors that may be co-expressed at the same synaptic terminal.

Synapse	Astrocyte
$[u_S, x_S, Y_S, \Gamma_S]$	$[I, h, C, \Gamma_A, x_A, G_A]$
$\dot{\Gamma}_S \equiv \dot{\Gamma}_S(G_A)$	$\dot{\Gamma}_A \equiv \dot{\Gamma}_A(Y_S)$
$\dot{u}_S = -\Omega_f u_S$	$\dot{I} = J_\beta(\Gamma_A(Y_S)) + \dots$
$\dot{x}_S = \Omega_d(1 - x_S)$	$\dot{C} = \dots$
$\dot{Y}_S = -\Omega_C Y_S$	$\dot{h} = \dots$
presynaptic Action Potential (AP)	$\dot{x}_A = \Omega_A(1 - x_A)$
	$\dot{G}_A = -\Omega_e G_A$
$u_0 = (1 - \Gamma_S)U_0^* + \alpha\Gamma_S$	Glio-Release Event - $C > C_\theta$ (GRE)
$u_S \rightarrow u_S + u_0(1 - u_S)$	
$r_S \rightarrow u_S x_S$	$r_A \rightarrow U_A x_A$
$x_S \rightarrow x_S - r_S$	$x_A \rightarrow x_A - r_A$
$Y_S \rightarrow Y_S + \rho_S Y_T r_S$	$G_A \rightarrow G_A + \rho_e G_T r_A$

Figure 1: **Computational scheme of presynaptic pathway of gliotransmitter modulation.** Synaptic variables with neurotransmitter time course (red) and astrocytic variables with gliotransmitter time course (green). The closed-loop gliotransmission ensues from "cross dependence" of  $G_A$  and  $Y_S$ . Mass balance equations for G-ChI model are reported in eqs (33) and (34).

In this study I want to go deeply into the analysis of presynaptic pathway of gliotransmission concerning the glutamate, in particular the effect of release-decreasing on presynaptic release probability.

## 1.1 Modulation of synaptic release

How the presynaptic release probability  $r_S$  is modulated by release-decreasing gliotransmission? The answer is set into equation (8), that explain how basal release probability changes in presence of astrocytic modulation.

Following the procedure presented in [4], I begin from the simplest situation: presynaptic neuron is a simple spikes generator, i.e. the spikes train is generated "by hand" and postsynaptic neuron only monitors excitatory conductance  $g_e$  directly connected to excitatory synapses. The core is what happens in the synaptic cleft, in presence of release-decreasing effect.

In open-loop circuit, only the astrocyte influences the synaptic dynamics whereby the onset of calcium oscillations and the gliorelease depends only on endogenous  $IP_3$  production. In Figure (2), indeed, the fraction of astrocytic binding with glutamate is always 0, while the  $I$  and  $C$  start to oscillate due to strong nonlinearity present in astrocytic dynamics (see equations (32), (33) and (34)).

The limit case of release-decreasing effect happens when  $\alpha$  is equals to 0, in this case the time course of basal synaptic release (8) becomes:

$$u_0 = (1 - \Gamma_S)U_0^* \quad (9)$$

The dynamic behavior of  $\Gamma_S$  characterizes the neurotransmitters release. After a gliorelease event (GRE) its value jumps into to range 0-1 and then falls back to zero as reported in Figure (3), thereby the released neurotransmitter per action potential is generally lower than in the "simple" synapses - decreasing effect -. This amount, due to exponentially decay, tends to increase at every action potential with respect to preceding one, a phenomenon called facilitation.

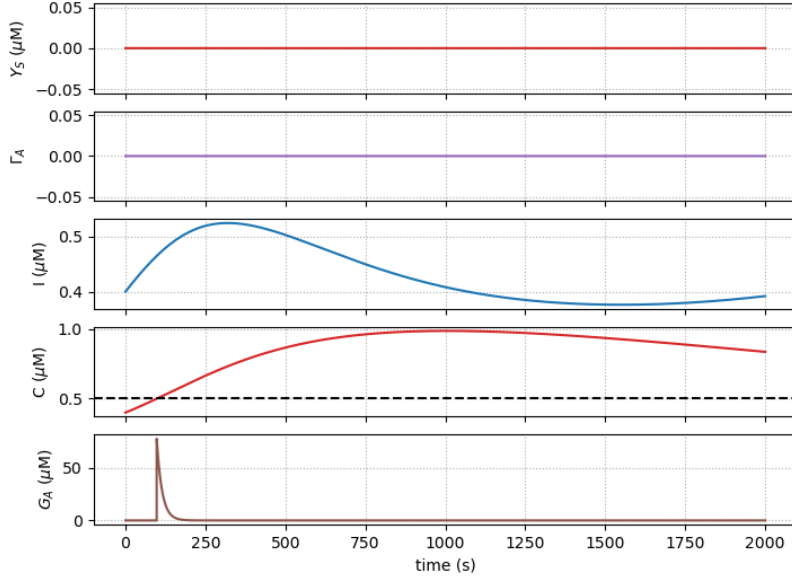


Figure 2: **Astrocytic variable dynamics in open-loop.** Astrocyte is not coupling with synapses whereby the fraction of binding receptor  $\Gamma_A$  is 0 (top panel) and the intracellular oscillations ( $I$  and  $C$ ) depend on endogenous mechanisms. The gliorelease events is strongly related with initial conditions of  $\text{Ca}^{2+}$  and  $\text{IP}_3$  concentration:  $I = 0.4$  and  $C = 0.4$  lead to GRE at 97.55 ms (bottom panel), time simulation is 2 seconds.

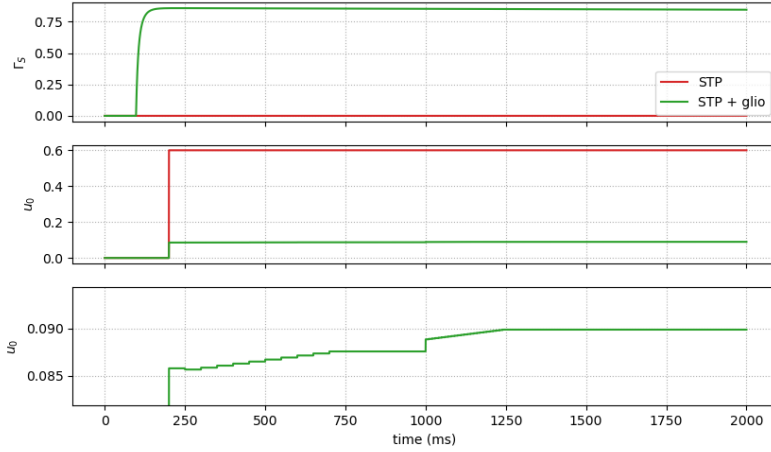


Figure 3: **Fraction of activated synaptic receptor and basal release probability in open-loop.** (top panel) Gliotransmitter release at time 97.55 ms triggers an increase of  $\Gamma_S$ , (middle panel) the notable effects is the decreasing of basal release probability  $u_0$  whose dynamics is connected with presynaptic action potential (bottom panel). The presynaptic spikes train is the same as in Figure (4).

Figure (4) illustrates how gliotransmitter release could changes synaptic neurotransmitter release in view of above consideration.

Presynaptic sample of spikes shows two different rate, 20 and 100 Hz. Without gliotransmission the extracellular neurotransmitter concentration  $Y_S$  progressively decreasing with the incoming action potentials (red traces), according to the depletion induced by STP. Taking into account gliorelease, indeed, leads

to *short-term facilitation*, that is a transient increase of neurotransmitter release during consecutive APs (green traces).

Postsynaptic conductance  $g_e$  basically has the same behavior of  $Y_S$ , i.e.  $g_e \rightarrow g_e + w_e r_S$ , for this reason the facilitation is present in the same way.

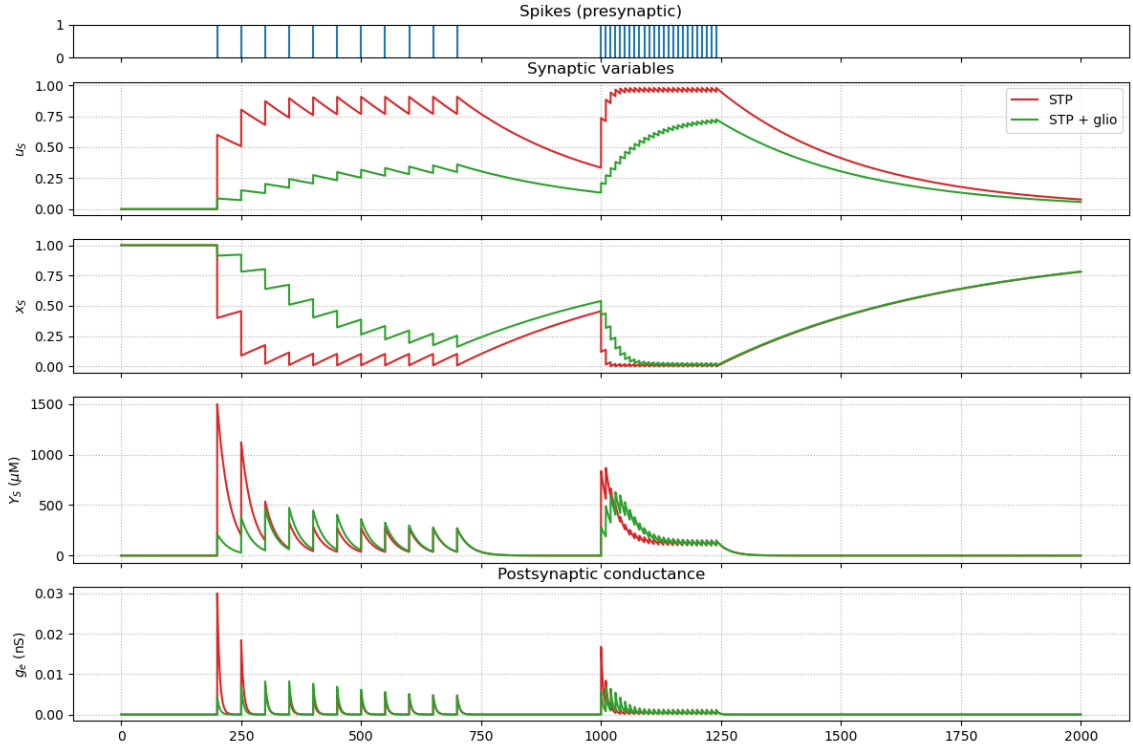


Figure 4: **STP facilitation in open-loop circuit.** (top panel) presynaptic sample of action potential, two different frequencies are present: 20 and 100 Hz. in both cases the facilitation effect is present, in particular with higher synaptic rate  $Y_S$  exceeds the correspondent values without gliotransmission. GRE happens at 97.55 ms while first AP arrives at 200 ms.

The facilitation effect is profoundly affected by the fraction of activated synaptic receptor by gliotransmitter  $\Gamma_S$ . It is plausible assume, looking equation (3), the concentration of gliotransmitter  $G_A$  influences the neurotransmitter release, i.e.  $r_S$ .

Figure (5) illustrates how the gliotransmission effects change with respect to the concentration of gliotransmitter released after a GRE ( $G_T$ ). An increase of  $G_T$  leads to an increase of gliotransmitter concentration in periastrcytic space  $G_A$ , thus the fraction on activated synaptic receptor increase, in other word the effect of gliotransmission on synaptic release is stronger. As a consequence of stronger gliotransmission, the basal release probability is brought close to 0 (top panel).

Short-term facilitation can be charaterized considering synaptic release due to pairs of APs, computing for each pair the paired-pulse ratio (PPR) of the fraction of neurotransmitter released by the first AP.

$$\text{PPR} = \frac{r_{S_{i+1}}}{r_{S_i}} \quad (10)$$

When  $\text{PPR} < 1$  the neurotransmitter released by the second AP is less than the amount released by the first AP (depression effect), coversely, if  $\text{PPR} > 1$  the synaptic release increases with incoming of action potential (facilitation effect). Looking at the middle and the bottom panel in Figure (5) emerge these considerations:

- Without gliotrasmission (index 0) the depletion is dominant and the only "facilitation event" at 1000 ms depends on time evolution of synaptic variable, in this case we talk about recovery-from-depression (RFD).
- With gliotrasmission (indeces 1,2 and 3) short-term facilitation is strongly present and the transient time where it happens increase with  $G_T$  (index 1 has higher values of index 3).

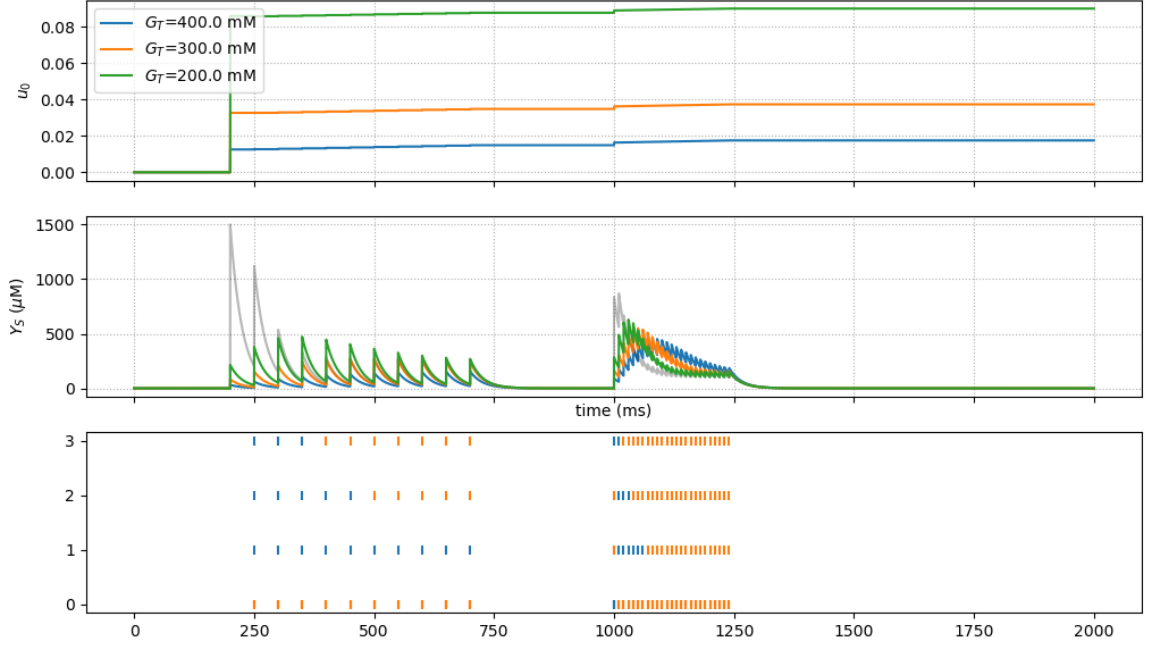


Figure 5: **STP facilitation with respect to  $G_T$  in open-loop circuit.** (Top panel) Increasing the gliotrasmitter release leas to an increase of  $\Gamma_S$ , as a consequence the basal release probability falls to 0. (middle panel) Neurotrasmitter relesed by consecutive APs shows differet behavior that can be quantified by PPR factor. (bottom panel) Every release event is colored in orange (depression) and in blue (facilitation), index 0 stand for the case without gliotrasmission while indeces 1, 2 and 3 are respectively the case of  $G_T = 400.0, 300.0$  and  $200.0 \mu M$ .

It is possible to consider a more realist situation with presynaptic spikes train come from Poisson distribu-  
tion. Also in this situation, as reported in Figure (6), the facilitation effect is stronger for higher values of  
gliotrasmitter release from astrocyte.

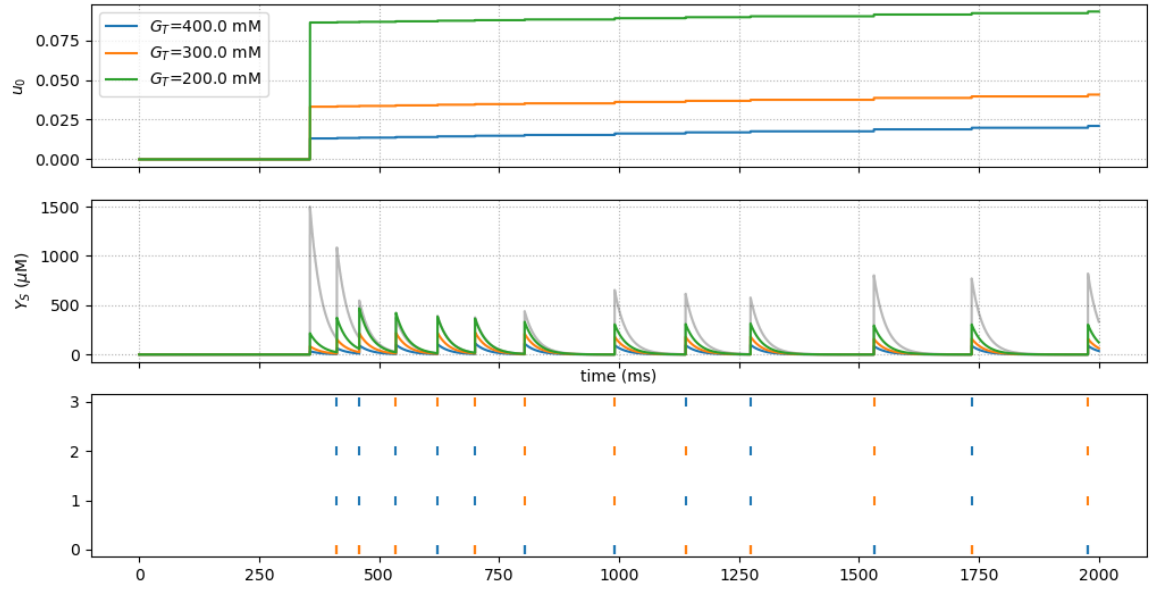


Figure 6: **STP facilitation with respect to  $G_T$  in open-loop circuit for Poisson presynaptic input.** The images are obtained with same conditios on Figure (5). A Poisson presynaptic spikes train with  $\nu_{in} = 3.5$  Hz substitutes the spikes train "by hand".

## 1.2 Closed- vs Open- Loop circuit

In previous discussion I only consider one-way interactions between synapse and astrocyte, the modulation of synaptic release by gliotransmission. However in general case the other possible pathway, the modulation of gliotransmission by synaptic release, may coexist with the other in so called closed-loop circuit.

The synaptic modulation triggers in astrocytes an addition mechanism of  $IP_3$  production depend on extracellular neurotransmitters concentration (see Figure (1)). This exogenous  $IP_3$  production changes the dynamics of  $I$  in the G-ChI model and, as a consequence, the  $Ca^{2+}$  oscillations.

Figure (7) describes the differences between open- and closed-loop scenario also in terms of gliorelease events (GRE). The main dynamic changes are found in the  $I$  time evolution (second panel), according to the onset of exogenous  $IP_3$  production and, for the strong nonlinear coupling with  $C$ , also the timing of GREs are profoundly affected (bottom panel).

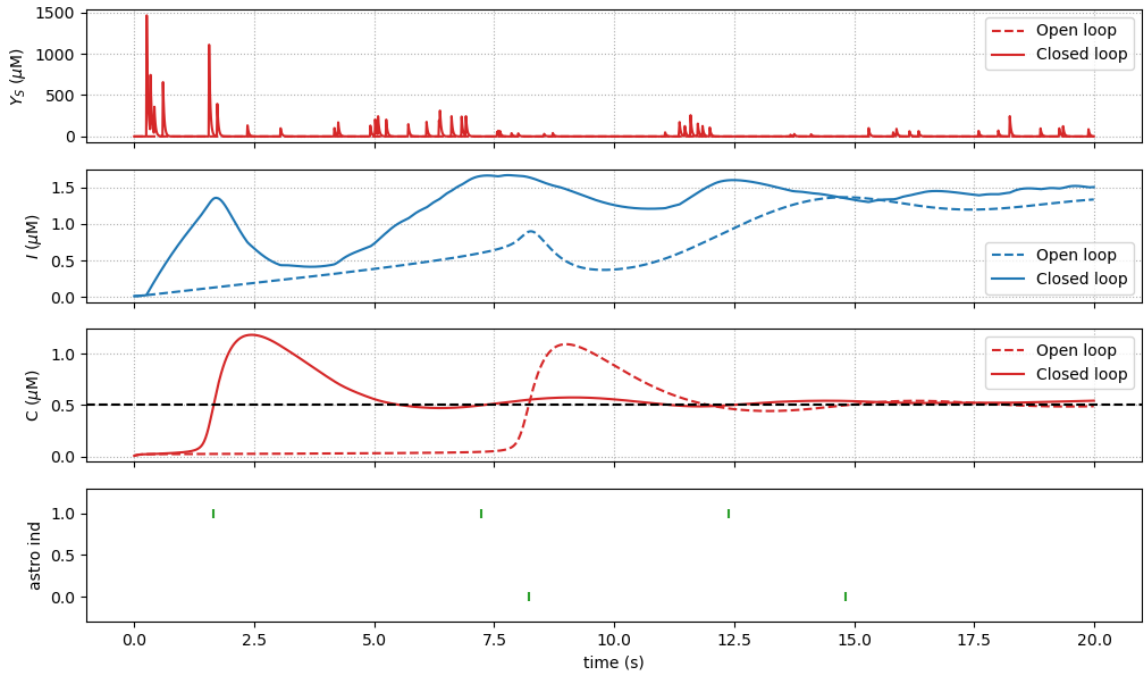


Figure 7: **Differences between astrocyte dynamics in open- and close- loop.** Astrocytes variable dynamics in open- (dashed) and closed-loop (solid) circuit. Exogenous  $IP_3$  production deeply changes the  $I$  time evolution and this is reflected in the GREs time distribution (bottom panel, 0 = open, 1 = closed). Initial conditions:  $I=C=0.01 \mu M$ ,  $h=0.9$ ,  $Y_S=0 \mu M$

To elucidate some of possible functional implications of closed-loop gliotransmission, the average synaptic release for  $N_{syn}=160$  identical synapses is computed for constant stimulus and compare it to the open-loop scenario as well as simple synapses without gliotransmission.

Figure (8) shows some simulations of gliotransmission for time evolution of average neurotransmitter concentration in the synaptic cleft in response to constant input rate<sup>1</sup>. Gliotransmission dramatically changes the synaptic transmission.

The facilitation effect is visible both for open and closed circuit, after a gliorelease event the neurotransmitter abruptly decrease (at 2 s, 8 s and 14 s for closed-loop and at 8 s and 15 s for open-loop) and then increasing according to facilitation effect. The notable differences are found in GRE distribution shows in right panel: while the astrocytes in open-loop fire at the same time, in closed-loop this distribution of GREs are sparse.

<sup>1</sup>Authors in [4] studied the responses to a steps function of incoming action potential to describe also the behavior or gliotransmission when the input changes during time simulation. Here I put myself in a simple situation



Also in this situation,  $\Gamma_S$  is the main protagonist of time evolution and, in particular, of the onset of facilitation effect.

In figure (9) there are different time courses with respect to  $\Omega_G$ , agonist release (deactivating) rate (see equations (3)). An increase of  $\Omega_G$  changes the exponential decay rate of  $\Gamma_S$ , such that both open and closed faster approximate the no gliotrasmission case, i.e.  $\Gamma_S$  equals to O (top rows in Figure (9)). This is clearly visible in the  $Y_S$  time evolution, with high  $\Omega_G$  its values is very similar to no gliotrasmission one. In principle might be exist a dependence with respect to  $G_T$ , but these simulations does not this behavior (data not shown).

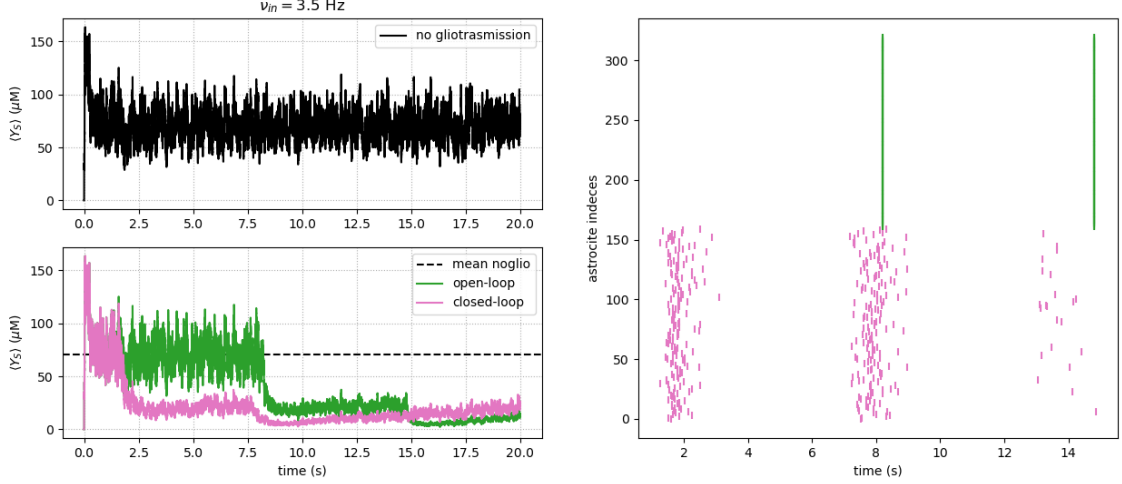


Figure 8: **Average neurotransmitter release in case of no gliotrasmission, open- and closed-loop.** (left panels) Average neurotransmitter release on 160 independent identical synapses for 20 seconds long simulation, presynaptic firing rate is 3.5 Hz. (right panel) Raster plot of GRE, astrocytes labeled from 0 to 160 (pink marker) are part of closed-loop, the other one (green) of open-loop. Initial conditions:  $I=C=0.01 \mu M$ ,  $h=0$ ,  $Y_S=0 \mu M$

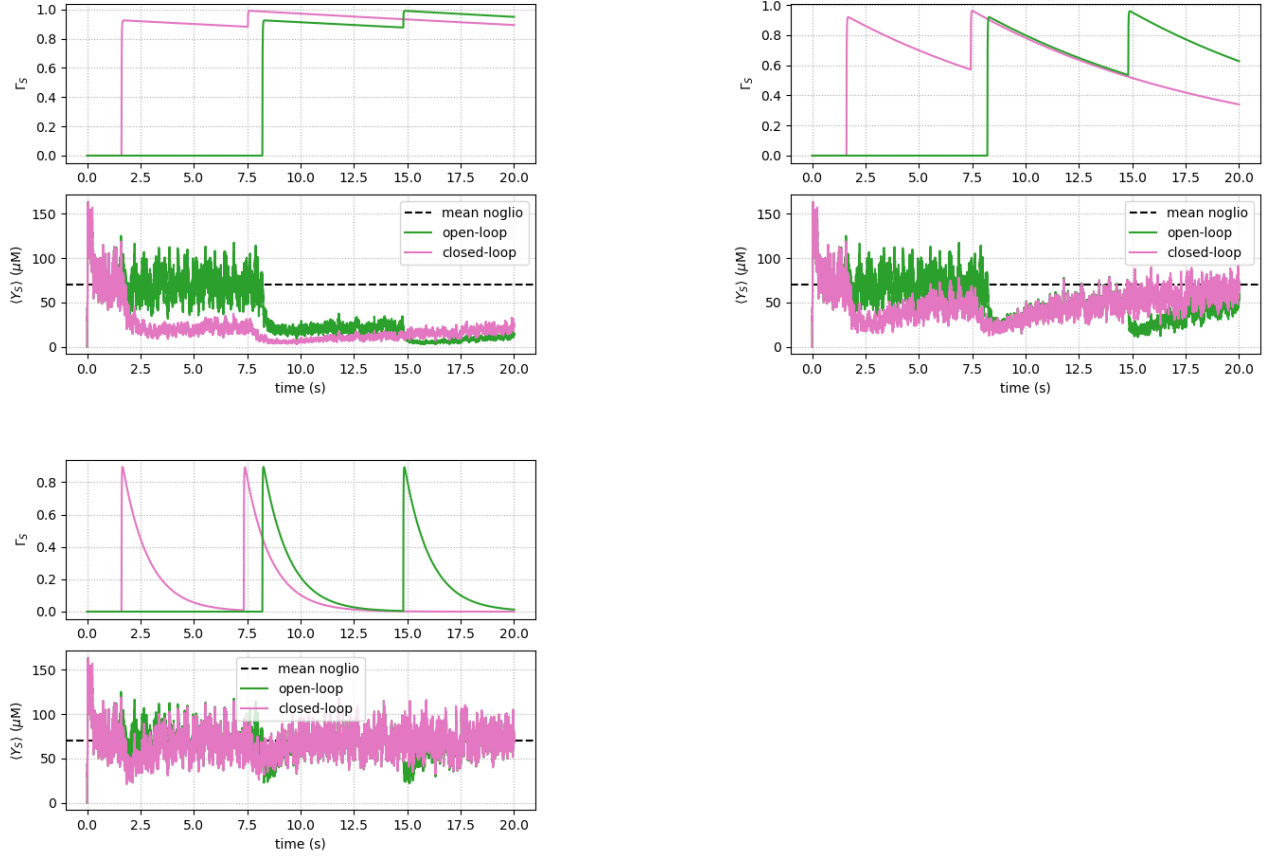


Figure 9: **Gliorelease effect with respect to  $\Omega_G$ .** Average neurotransmitter release on 160 independent identical synapses for 20 seconds long simulation. (top left)  $\Omega_G = 0.0083$  Hz; (top right)  $\Omega_G = 0.0833$  Hz; (bottom left)  $\Omega_G = 0.8333$  Hz.

The differences in terms of modulation effects between open- and closed-loop are further elucidated looking at the average synaptic release for different rates of randomly incoming action potentials. In this way it may be possible to analyse the nature of filtering behavior in presence of gliotransmitters release.

The low-pass filter characteristics of synapses without gliotransmission is visible in top left panel in Figure (10), with low presynaptic firing rate the inter-spikes interval (ISI) are big enough to allow the restoring of synaptic resources, the average of  $r_S$  perhaps is equal to 0.6 namely the value in absence of plasticity. For higher firing rate, instead, the synaptic depletion leads to decrease  $r_S$ .

In closed-loop circuit, the nature of filtering characteristics changes into a band-pass filter (bottom left in Figure (10)). A qualitative explanation may be found into the combination of release-decreasing and facilitation effects:<sup>2</sup>

- low presynaptic rates (less than 0.8 Hz). As the no gliotransmission situation, the inter-spikes interval is big enough to allow the recovering of synaptic resources. In addition the low synaptic activity makes the astrocytic variables in a range close to gliorelease threshold (left column in Figure (12)), thus the gliorelease events are relative close to each others as shown in raster plot in Figure (10). The consequences is, according to the previous discussions,  $\Gamma_S$  lies in a range close to 1, thus for equation (9) basal release probability is strongly close to 0 due to release-decreasing effect. In conclusion the mean of  $r_S$  is lower than no gliotransmission scenario.
- middle presynaptic rates (from 0.8 Hz to 3.5 Hz). Increasing the presynaptic firing rate leads to increase both neurotransmitter concentration into the synaptic cleft and the antagonist binding-receptor

<sup>2</sup>Authors in [4] studied more general systems. To tacking into account the possible interaction between two astrocytes, a further term of exogenous  $IP_3$  production is added into equation (32) stands for the possible  $IP_3$  diffusion through gap junction. Their filtering characteristics are slightly differnt from the simple situation where astrocyte-to-astrocyte connections are neglected.

of astrocyte. The exogenous production of  $IP_3$  is stronger than low presynaptic input rates, thus the steady state of  $I$  and  $C$  are higher (middle column in Figure (12)). The notable consequence is that the time between two consecutive gliotransmitter release are big enough to allow  $\Gamma_S$  to decrease. For this the facilitation effect is triggered and  $r_S$  increases.

- high presynaptic rates (greater than 10 Hz). For high input rates the synapses cannot sustain further gliotransmission release (right column in Figure (12)), thus the synaptic transmission becomes independent of gliotransmission as if it were in simple scenario without gliotransmission.

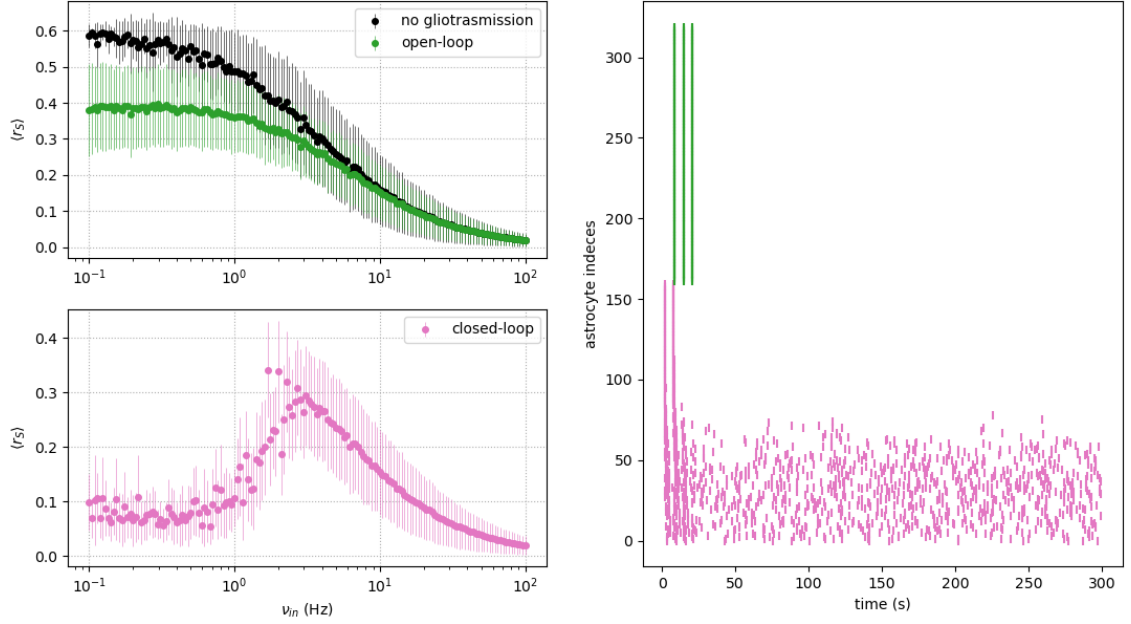


Figure 10: **Average release probability for different incoming action potential.** Average of  $r_S$  of 160 independent synapses for the three different situation, time simulation covers 300 second for each synapse but only the data after 50 seconds are taken to evaluate mean and standard deviation, integration steps is 1 ms. (top left) No gliotransmission and open-loop situation, there are no differences of filtering behavior. (bottom left) The two-pass filter becomes a band-pass filter in closed-loop circuit due to the combination of release-decreasing and facilitation effects. (right panel) GREs raster plot about open (green) and closed (pink) situation.

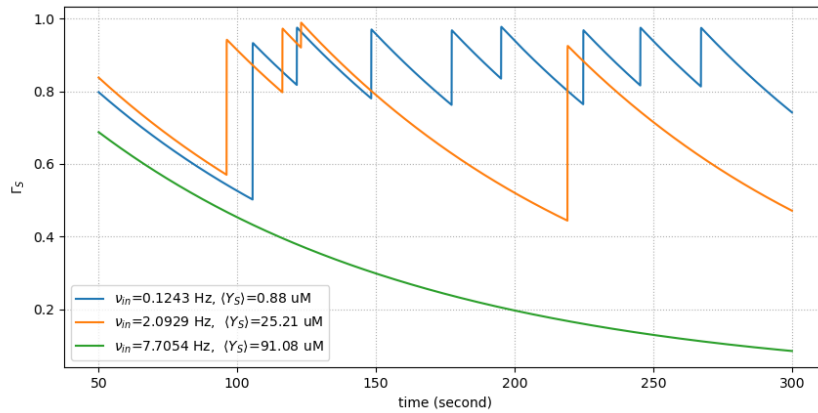


Figure 11: **Time evolution of synaptic variable in  $r_S$  modulation.** Time evolution  $\Gamma_S$  is intimate related to the onset of facilitation, the combination of its time course and the incoming action potential rates define the filtering behavior. Input rate: 0.12 (blue), 2.09 (orange) and 7.7 Hz (green)

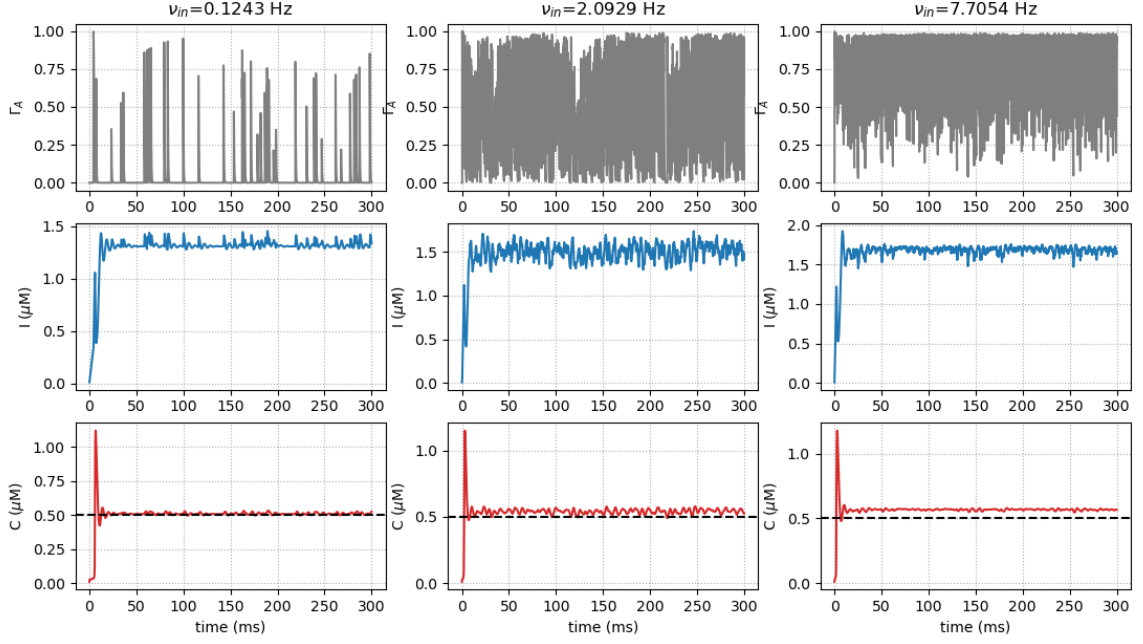


Figure 12: **Astrocyte dynamics with three different incoming action potential rates.**

### 1.3 Local circuit of the Network

In conclusion, to better understand the functional implication of gliotransmission and the effects that could have into the excitatory inhibitory neuronal network, I have studied the time evolution of postsynaptic neuron connected with 160 presynaptic excitatory inputs.

The goal is to compute the postsynaptic conductance  $g_e$  without gliotransmission and in presence of closed loop and compare their with results pf previous section. In addition it is possible to compute also the average neurotransmitter release from the  $g_e$  data using the follow equations:

$$\begin{aligned}\overline{\Delta g_e} &= \frac{1}{N_{tot}} \sum_{K,k} w_e r_S(t_k^K) \\ \overline{r_{S_{exc}}} &= \frac{\overline{\Delta g_e}}{w_e}\end{aligned}\tag{11}$$

where  $t_k^K$  is the  $k$ -th spike timing of excitatory presynaptic neuron  $K$ . From this data it is possible to have another prove of filtering behavior of synapses in realistic situation.

The presynaptic spikes train comes from 160 identical synapses fire in Poisson fashion with identical input rate. The data about the average neurotransmitters release are computed through (11) over a total time simulation of 250 seconds but the mean are computed only after 5 seconds. The results of  $\overline{r_{S_{exc}}}$  are collected in the following table:

$\nu_{in}$ (Hz)	$\overline{r_{S_{exc}}}$	
	no gliotrasmission	closed-loop
0.12	0.58	0.08
2.09	0.43	0.26
3.00	0.39	0.29
7.70	0.29	0.25
30.00	0.20	0.18
100.00	0.12	0.11

Table 1:  $\overline{r_{S_{exc}}}$  for 250 seconds long time simulation with 5 seconds transient time

Even if the low amount of data it is clear that the filtering characteristics are preserved. Without gliotrasmission, indeed, the neurotransmitters release decreases while, in closed-loop this values reaches a maximum at 3.00 Hz according to results shown in Figure (10). Nevertheless it is important to underling that this filtering features, at least for this particular set of parameters, emerge for long observation (simulation) time, that is the time windows where we can appreciate the facilitation effects. If the data are recorded only for 50 seconds or less,  $\Gamma_S$  has not enough time to restore itself and the facilitation is strongly attenuated (see Figure (13)), and this attenuation provides an underestimation of neuritransmitter release. Accordingly,  $\overline{r_{S_{exc}}}$ , for 50 seconds long simulation time and without transient, assumes the values in Table (2):

$\nu_{in}$ (Hz)	$\overline{r_{S_{exc}}}$	
	no gliotrasmission	closed-loop
0.12	0.58	0.10
2.09	0.40	0.11
3.00	0.35	0.12
7.70	0.21	0.12
30.00	0.10	0.07
100.00	0.05	0.04

Table 2:  $\overline{r_{S_{exc}}}$  for 50 secodns long time simulation without transient time

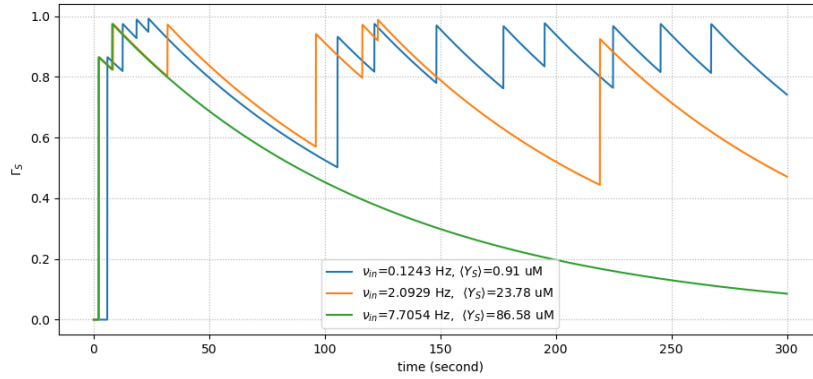


Figure 13: **Time evolution of synaptic variable in  $r_S$  modulation, no transient time.** Same plots as in Figure (11) without transient time. Because of the characteristic time constant of  $\Gamma_S$ , during the first 50 seconds the facilitation effects is strongly attenuated.

Last open question concern how the postsynaptic excitatory conductance is modulated by gliotrasmission. The aswer of this question is found into the combination of all above conclusion, Figure (14) summarises all the concepts that are elucidated before and helps us to get some notable insights about the neuro-glia interactions at network level.

Postsynaptic conductance  $g_e$  has got the same dynamics of  $Y_S$ , a exponential clearance combined with a steps increase at action potential arrival. For this reason release decreasing effect and short-term facilitation are both present as reported in Figure (8).

In presence of gliotransmission the value of  $g_e$  is always lower then in simple synapses (respectively pink and black traces in left column in Figure (14)) but, especially when  $\nu_{in}$  is close to the maximum of bell-shape curve (middle row), tends to recovery the value fixed by simple scenario, according to the facilitation effects.

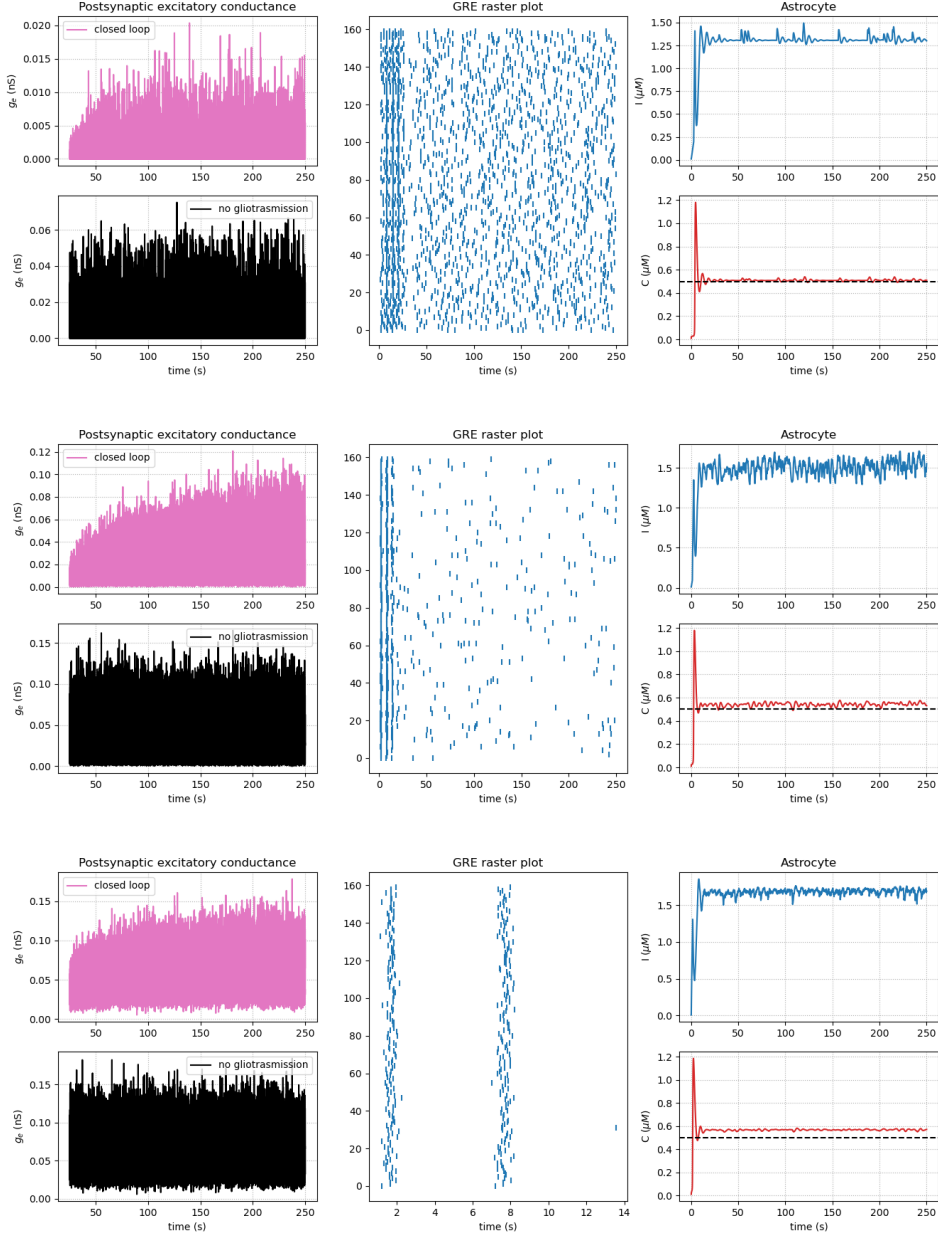


Figure 14: **Postsynaptic excitatory conductance dynamics with respect three different input rate.** Postsynaptic neurons, both in no gliotransmission and closed loop circuit are connected with 160 presynaptic (excitatory) synapses each of them fire with equal rate. The simulations run for 250 seconds (integration step is 0.5 ms) for each value of input rate: 0.12 Hz (top), 2.09 Hz (middle) and 7.70 Hz (bottom). The  $g_e$  in gliotransmission modulation (pink traces) are always lower than in simple synapses (black traces) according to release-decreasing effect, furthermore in the first case the value tends to increase (facilitation effects) in time "trying to reach" the maximum value fixed by simple scenario. GRE raster plots and the dynamics of astrocyte variable are equals to above discussion.

All the considerations emerged (if correct) in this report could be useful to set the right computational setting of neuron-glia network. First of all, with constant external input rate, the total time simulation

might be long enough to appreciate the short-term facilitation, namely at least 100 seconds with transient time of 20-30 seconds to avoid the bias introduced by initial conditions. In addition, the increasing in time of postsynaptic conductance might give an notable insight about how the modulation induced by astrocytes could be restored the balance between excitatory and inhibitory recurrent inputs during the network dynamics.

## 1.4 Mean field derivation of dynamical synapses

The phenomenological models of dynamical synapses can be used to analyse the way activity of large population of presynaptic neurons is transmitted to postsynaptic target. The model equations in (1) can be manipulated to derived a mean field description of synaptic dynamics, and thus of short-term plasticity. Furthermore the following methods could be generalized to derive an approximation also in presence of gliotransmission (see reference [5]).

The equation of dynamical synapses could be seen composed by two part: the time evolution between two consecutive spikes and what happens upon arrival of a generic spike. For instance before the first spike, i.e.  $[t_0, t_1)$ , the synaptic variable evolves according to:

$$\begin{aligned}\frac{du_S}{dt} &= -\Omega_f u_S \\ \frac{dx_S}{dt} &= \Omega_d(1 - x_S)\end{aligned}\tag{12}$$

This equations describe the time course of synaptic variable at the same time before the spikes, with this regards the variable could be replaced by  $u_S^-$  and  $x_S^-$ . The spikes arrival triggers the increase of release probability and the release of neurotransmitter resources, thus at time  $t_1$ :

$$\begin{aligned}u_S^+ &= u_S^- + u_0(1 - u_S^-) \\ r_S(t_1) &= u_S^+ x_S^- \\ x_S^+ &= x_S^- - u_S^+ x_S^-\end{aligned}\tag{13}$$

To generalize the above consideration, the dynamics with generic spikes train is completely described by the following set of equations:

$$\begin{aligned}\frac{du_S^-}{dt} &= -\Omega_f u_S^- + u_0 \sum_k (1 - u_S^-) \delta(t - t_k) \\ \frac{dx_S^-}{dt} &= \Omega_d(1 - x_S^-) - \sum_k u_S^+ x_S^- \delta(t - t_k) \\ u_S^+ &= u_S^- + u_0(1 - u_S^-)\end{aligned}\tag{14}$$

Equations (14) is a nonlinear system of two ODEs, substituting the third expression into the first one provides:

$$\begin{aligned}\frac{du_S^+}{dt} &= \Omega_f(u_0 + u_S^+) + u_0 \sum_k (1 - u_S^+) \delta(t - t_k) \\ \frac{dx_S^-}{dt} &= \Omega_d(1 - x_S^-) - \sum_k u_S^+ x_S^- \delta(t - t_k)\end{aligned}\tag{15}$$

To simplify the notation, I following redefine the variable without the + and - apexes.

Consider then  $n_S$  trials of stimulation of a synapse by trains of APs of equal length and same statistics, delivered to the synapse at identical initial conditions. The trial-averaged synaptic dynamics for the mean AP is described by equations (15) in term of mean quantities  $\bar{u}_S = 1/n_S \sum_l^{n_S} u_{S_l}$  and  $\bar{x}_S = 1/n_S \sum_l^{n_S} x_{S_l}$ ,

$$\begin{aligned}\frac{d\bar{u}_S}{dt} &= \Omega_f(u_0 + \bar{u}_S) + \frac{u_0}{n_S} \sum_l^{n_S} \sum_k (1 - u_{S_l}) \delta(t_{k_l}) \\ \frac{d\bar{x}_S}{dt} &= \Omega_d(1 - \bar{x}_S) - \frac{1}{n_S} \sum_l^{n_S} \sum_k u_{S_l} x_{S_l} \delta(t_{k_l})\end{aligned}\tag{16}$$

In a small time interval  $\Delta t$ , the above equations can be rewritten in terms of finite differences as:

$$\begin{aligned}\bar{u}_S(t + \Delta t) - \bar{u}_S(t) &= \Omega_f(u_0 + \bar{u}_S)\Delta t + \frac{u_0}{n_S} \sum_l^{n_S} (1 - u_{S_l}) \Delta_l(\Delta t) \\ \bar{x}_S(t + \Delta t) - \bar{x}_S(t) &= \Omega_d(1 - \bar{x}_S)\Delta t - \frac{1}{n_S} \sum_l^{n_S} u_{S_l} x_{S_l} \Delta_l(\Delta t)\end{aligned}\tag{17}$$

where  $\Delta_l(\Delta t) = \sum_k \delta(t - t_{l_k})\Delta t$  is the number of spikes in the time interval  $\Delta t$  for the  $l$ th trial and is a strongly stochastic quantity.

Analysis of neurophysiological data revealed that individual neurons in vivo fire irregularly at all rates, reminiscent of a Poisson process. Mathematically, the Poisson assumption means that, at each moment, the probability that a neuron fires equals the neuron's instantaneous firing rate and is independent of the timing of previous APs. Then, assuming that the  $n_S$  trains of APs under consideration are different realizations of the same Poisson process with average rate  $\nu_S(t)$ , equations (17) can be averaged in time over a proper  $\Delta t$ . In particular, thanks to the Poisson hypothesis, the variable  $u_S$ ,  $x_S$ ,  $u_S x_S$  and  $\Delta_l(\Delta t)$  can be consider independent and thus be averaged independently.

Therefore, taking  $\Delta t$  of an order of several intervals between spikes, but shorter than longest time scale in the system ( $1/\Omega_d$  and  $1/\Omega_f$ ), the time average (denoted by  $\langle x \rangle$ ) of  $\Delta_l(\Delta t)$  can be estimate by  $\Delta_l(\Delta t) = \nu_S(t)\Delta t$ . Accordingly,

$$\begin{aligned}\langle \bar{u}_S(t + \Delta t) \rangle - \langle \bar{u}_S(t) \rangle &= \Omega_f(u_0 + \langle \bar{u}_S \rangle)\Delta t + \frac{u_0}{n_S} \sum_l^{n_S} (1 - \langle u_{S_l} \rangle) \nu_S(t)\Delta t \\ \langle \bar{x}_S(t + \Delta t) \rangle - \langle \bar{x}_S(t) \rangle &= \Omega_d(1 - \langle \bar{x}_S \rangle) - \frac{1}{n_S} \sum_l^{n_S} \langle u_{S_l} x_{S_l} \rangle \nu_S(t)\Delta t\end{aligned}\tag{18}$$

Finally, divided by  $\Delta t$  yields

$$\begin{aligned}\frac{d\langle \bar{u}_S \rangle}{dt} &= \Omega_f(u_0 + \langle \bar{u}_S \rangle) + u_0(1 - \langle \bar{u}_S \rangle) \nu_S(t) \\ \frac{d\langle \bar{x}_S \rangle}{dt} &= \Omega_d(1 - \langle \bar{x}_S \rangle) - \langle \bar{u}_S \rangle \langle \bar{x}_S \rangle \nu_S(t)\end{aligned}\tag{19}$$

that is a nonlinear and nonautonomous set of two ODEs and describe the dynamics of average synaptic variables. In general it is possible to resolve analytically the first equations and then, putting the results in the second, resolve the whole system. However, when the presynaptic firing rate is constant in time, i.e.  $\nu_S(t) = \nu_S$ , the system becomes autonomous and it is possible to evaluate the steady states. Accordingly, the intersection of nullclines provides the fixed points for the systems:

$$\begin{aligned}\langle \bar{u}_S \rangle &= \frac{u_0(\Omega_f + \nu_S)}{\Omega_f + \nu_S u_0} \\ \langle \bar{x}_S \rangle &= \frac{\Omega_d}{\Omega_d + \langle \bar{u}_S \rangle \nu_S}\end{aligned}\tag{20}$$

Now it is easy to estimate the behavior with extreme values of presynaptic firing rate. In presence of low firing rate, i.e.  $\nu_S \rightarrow 0$ , the probability of release tends to  $u_0 = 0.6$  and the available neurotransmitter resourses tends to 1, thus the  $r_S = u_S x_S \rightarrow u_0$ . Conversely for high firing rate, i.e.  $\nu_S \rightarrow +\infty$ ,  $u_S$  tends to 1 and  $x_S$  tends to 0, therefore the average values of neurotransmitter is 0.

This conclusion are in totally agreement with the qualitative discussion about the filtering behavior of simple synapse. In addition, the approximate solution of  $r_S = u_S x_S$  shown in Figure (15) is similar to numerical solution presented in Figure (10).



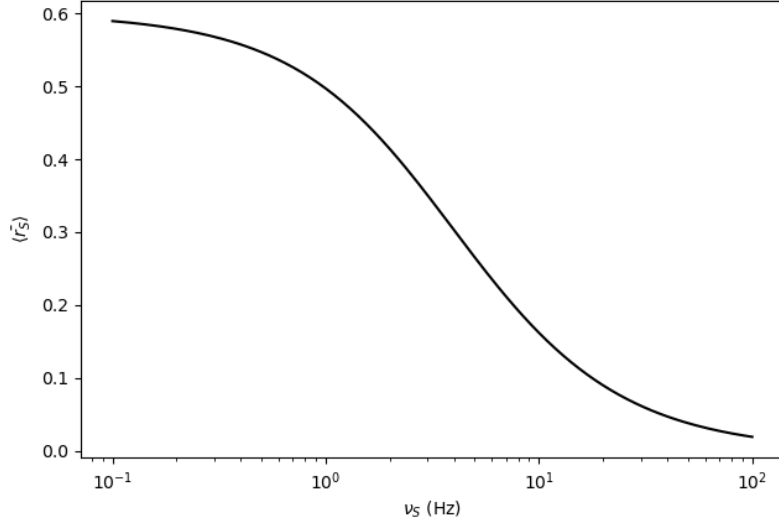


Figure 15: **Mean field approximation solution of released neurotransmitter in simple synapses.** Approximation solution of average value of  $r_S$ .

### Questions about Mean field STP

The author in [3] writes down a similar set of equations describing the dynamical synapses:

$$\begin{aligned}
 \frac{du_S^+}{dt} &= -\Omega_f u_S^+ + u_0 \sum_k (1 - u_S^+) \delta(t - t_k) \\
 \frac{dx_S^-}{dt} &= \Omega_d (1 - x_S^-) - \sum_k u_S^+ x_S^- \delta(t - t_k) \\
 u_S^- &= u_S^+ + u_0 (1 - u_S^+)
 \end{aligned} \tag{21}$$

The differences are in the first and in the last equations where  $u_S^-$  in (14) becomes  $u_S^+$ . Then, substituting  $u_S^+$  into the first equations the final set is equals to (16) and the conclusion is the same. I don't understand the mathematics beyond this kind of procedure.

- Equations in (21) provide the following relation between  $u_S$  just before and after a spikes:

$$u_S^+ = \frac{u_S^- - u_0}{1 - u_0} \tag{22}$$

At very beginning, when  $u_S^-$  is 0, this leads to a negative values for  $u_S^+$  and this is impossible because the probability is in range 0 and 1.

### 1.5 Mean field description of Gliotrasmission modulation

A mean field description of gliorelease events could be found following the same procedure of neurotransmitter release, noting that a release event by astrocyte is described by same model of synaptic release, i.e. TM model.

With this aim the first important observation is that nucleation of spontaneous spikes in astocyte, namely in case on open-loop circuit, may be approximated by a Poisson process with time-dependent frequency  $\nu_A(t)$ . In general, the exact expression of the GRE rate is not crucial for the validity of mean field derivation, what is crucial is the Poisson assumption. The mean field equivalent of equations (4) and (5) reads as:

$$\begin{aligned}
 \frac{d\langle \bar{x}_A \rangle}{dt} &= \Omega_A (1 - \langle \bar{x}_A \rangle) - U_A \langle \bar{x}_A \rangle \nu_A(t) \\
 \frac{d\langle \bar{G}_A \rangle}{dt} &= -\Omega_e \langle \bar{G}_A \rangle + \rho_e G_T U_A \langle \bar{x}_A \rangle \nu_A(t)
 \end{aligned} \tag{23}$$

In particular, experimental data suggest that the timescale of gliotransmitter modulation is much slower than the time course of gliotransmitter in the ECS. Accordingly, it may be assumed that  $\Omega_G \ll \Omega_A, \Omega_e$ , and only the timescale slower than  $1/\Omega_e$  can be considered in second equations (23) so that:

$$\langle \bar{G}_A \rangle \approx \frac{\rho_e G_T}{\Omega_e} U_A \langle \bar{x}_A \rangle \nu_A(t) \quad (24)$$

Substituting the above equation in (3), and averaging the latter, provides:

$$\begin{aligned} \frac{d\langle \bar{\Gamma}_S \rangle}{dt} &= J_S U_A \langle \bar{x}_A \rangle (1 - \langle \bar{\Gamma}_S \rangle) \nu_A(t) - \Omega_G \langle \bar{\Gamma}_S \rangle \\ J_S &= \rho_e \frac{O_G G_T}{\Omega_e} \end{aligned} \quad (25)$$

The above equations can generally be used to reliably estimate the mean field dynamics of basal release probability

$$\langle \bar{u}_0 \rangle = U_0^* + (\alpha - U_0^*) \langle \bar{\Gamma}_S \rangle \quad (26)$$

In conclusion the equations (23), (25) and (26) provide a mean field description of gliorelease event and the modulation of basal release probability by astrocyte. For constant astrocytic firing rate, i.e.  $\nu_A(t) = \nu_A$  is relevant considering the steady state solution of  $\langle \bar{x}_A \rangle$ ,  $\langle \bar{\Gamma}_S \rangle$  and  $\langle \bar{u}_0 \rangle$ .

$$\begin{aligned} \langle \bar{x}_A \rangle &= \frac{\Omega_A}{\Omega_A + U_A \nu_A} \\ \langle \bar{\Gamma}_S \rangle &= \frac{J_S \Omega_A U_A \nu_A}{\Omega_A \Omega_G + (J_S \Omega_A + \Omega_G) U_A \nu_A} \end{aligned} \quad (27)$$

For low astrocytic firing rate,  $\nu_A \rightarrow 0$ , the gliotransmitter resources tends to 1 and the fraction of presynaptic receptors tends to 0, thus the neurotransmitter modulation by astrocyte does not modify the basal release probability. For higher  $\nu_A \rightarrow +\infty$ , instead,  $x_A$  tends to 0 while  $\Gamma_S$  approaches to its limit value  $J_S \Omega_A / (J_S \Omega_A + \Omega_G) = 0.9957$ , in this situation the modulation is stronger than anything else and the basal probability tends to 0.

Figure (16) show the behavior of basal release probability for release-decreasing ( $\alpha = 0$ ), in particular  $\langle \bar{u}_0 \rangle$  decreases with increasing  $\nu_A$ , according to the consideration about the results in Figures (10) and (11)

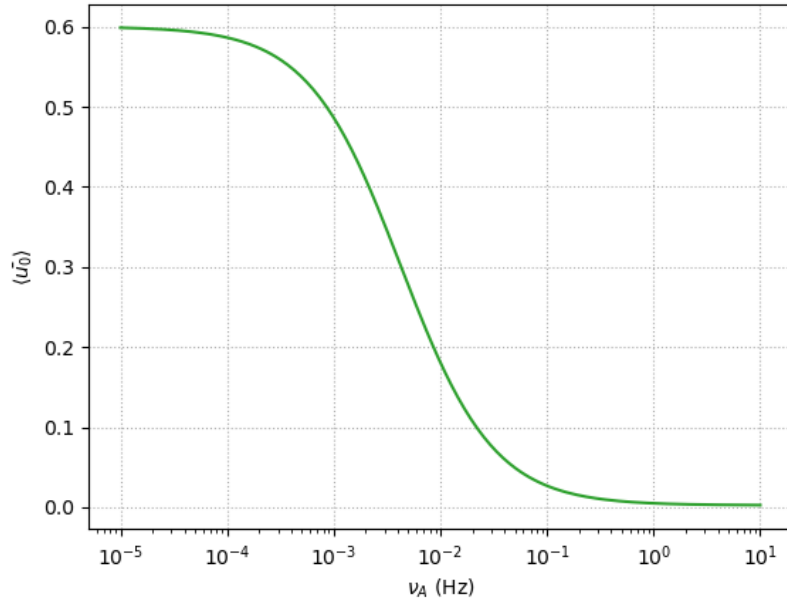


Figure 16: **Mean field approximation solution of gliotransmitter modulation.** Approximation solution of average value of  $r_S$ .

## 1.6 Mean Field description of Closed-loop

The considerations of above paragraphs naturally lead us to consider the ensemble of equations (19), (23), (25) and (26) as a mean field description of synaptic transmission in the presence of gliotransmission:

$$\begin{aligned}
\frac{d\langle \bar{u}_S \rangle}{dt} &= \Omega_f(u_0 + \langle \bar{u}_S \rangle) + \langle \bar{u}_0 \rangle(1 - \langle \bar{u}_S \rangle)\nu_S(t) \\
\frac{d\langle \bar{x}_S \rangle}{dt} &= \Omega_d(1 - \langle \bar{x}_S \rangle) - \langle \bar{u}_S \rangle \langle \bar{x}_S \rangle \nu_S(t) \\
\frac{d\langle \bar{x}_A \rangle}{dt} &= \Omega_A(1 - \langle \bar{x}_A \rangle) - U_A \langle \bar{x}_A \rangle \nu_A(t) \\
\frac{d\langle \bar{\Gamma}_S \rangle}{dt} &= J_S U_A \langle \bar{x}_A \rangle (1 - \langle \bar{\Gamma}_S \rangle) \nu_A(t) - \Omega_G \langle \bar{\Gamma}_S \rangle \\
\langle \bar{u}_0 \rangle &= U_0^* + (\alpha - U_0^*) \langle \bar{\Gamma}_S \rangle
\end{aligned} \tag{28}$$

Basically, starting from the mean description of dynamical synapse when  $u_0$  is constant, now we consider the astrocytic modulation of this parameters introducing its dynamical behavior. This could be done if the intrinsic dynamic of  $u_0$  is considered independent by  $u_S$  and  $x_S$  so that, in the derivation of (19), it is a simple constant. This assumption is completely satisfied in case of open-loop scenario, when the astrocytic variable dynamics, in particular  $x_A$ , does not depends on neurotransmitter concentration in ECS.

The situation is more complicated in the case of closed-loop, when the bidirectional coupling between astrocyte and synapses must be taking into account, in this case indeed  $x_A$  depends on synaptic release. However, the independent assumption of  $u_0$  is not completely out of sense because equations (25) and (26) tell us  $u_0$  depends on  $x_A$  only through the exogenous production of  $\text{IP}_3$  in astrocytic dynamical equations (see Appendices). The other import assumption that must be satisfied is the GREs, also in presence of bidirectional coupling, can be approximated by a Poisson process.<sup>3</sup> The last step to complete the mean field description in closed-loop is to exploit the coupling features, this provides a dependence of  $\nu_A(t)$  on  $\nu_S(t)$ , thus the only parameters that drive the system is the presynaptic firing rate. From equations (20) and (27) the steady states of mean field description in closed-loop scenario are:

$$\begin{aligned}
\langle \bar{u}_S \rangle &= \frac{u_0(\Omega_f + \nu_S)}{\Omega_f + \nu_S u_0} \\
\langle \bar{x}_S \rangle &= \frac{\Omega_d}{\Omega_d + \langle \bar{u}_S \rangle \nu_S} \\
\langle \bar{x}_A \rangle &= \frac{\Omega_A}{\Omega_A + U_A \nu_A(\nu_S)} \\
\langle \bar{\Gamma}_S \rangle &= \frac{J_S \Omega_A U_A \nu_A(\nu_S)}{\Omega_A \Omega_G + (J_S \Omega_A + \Omega_G) U_A \nu_A(\nu_S)}
\end{aligned} \tag{29}$$

To complete the analytic expression of closed-loop circuit this relation must be derive from astrocytic and synaptic dynamics. However, Figure (14) shows that  $\nu_A$  decreases with increasing of  $\nu_S(t)$  and guides us to formulate a "guess" expression of  $\nu_A \equiv \nu_A(\nu_S)$ :

$$\nu_A = A e^{(-\nu_S)} \tag{30}$$

Where  $A$  is the maximum astrocytic firing rate. Figure (17) illustrates the steady state of neurotransmitter resources in presence of gliotransmission with the guess function in equations (30), the bell-shape of left panel resembles the filtering characteristics in Figure (10).

<sup>3</sup>The only clue that brings me to consider valid this assumption comes from the evidence that the suprathreshold oscillations of  $\text{Ca}^{2+}$  are generated by  $Y_S$  that follows a Poisson process.

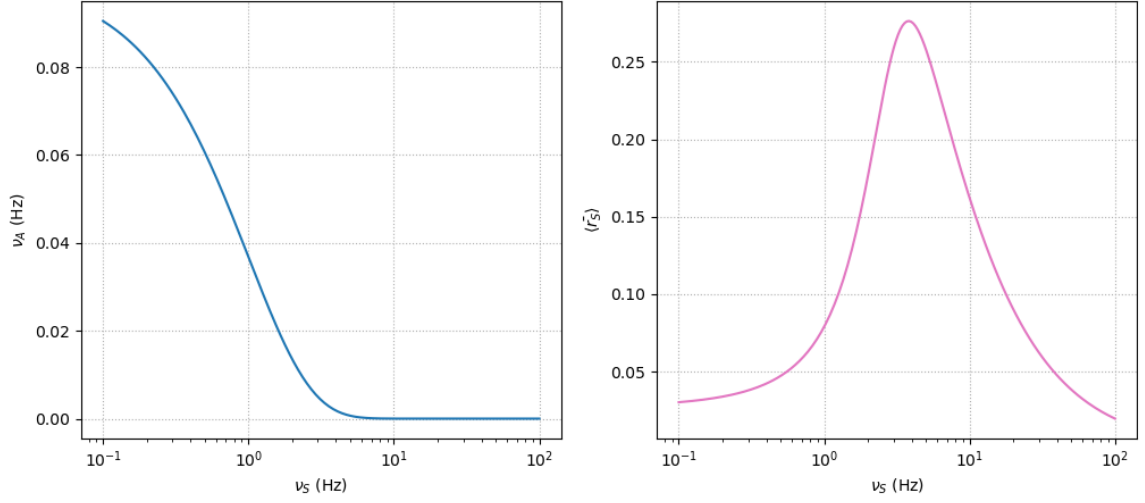


Figure 17: **Mean field solution of closed-loop gliotransmission.** (left panel)  $\nu_A(\nu_S)$  with exponential decreasing guess function,  $A = 0.1$  Hz. (right panel) Steady states of neurotransmitter release with respect to presynaptic firing rate.

The exponential guess function in (30) comes from qualitative description of filtering characteristic curve of closed-loop scenario and also from numerical in Figure (18). Going deeply into the relation between astrocytic and synaptic firing rate it is possible to underline meaningful information. Figure (18), indeed, shows an increasing of  $\nu_A$  before the exponential decay. Thus guess function might be correct to describe new type of dynamics for low synaptic frequency.

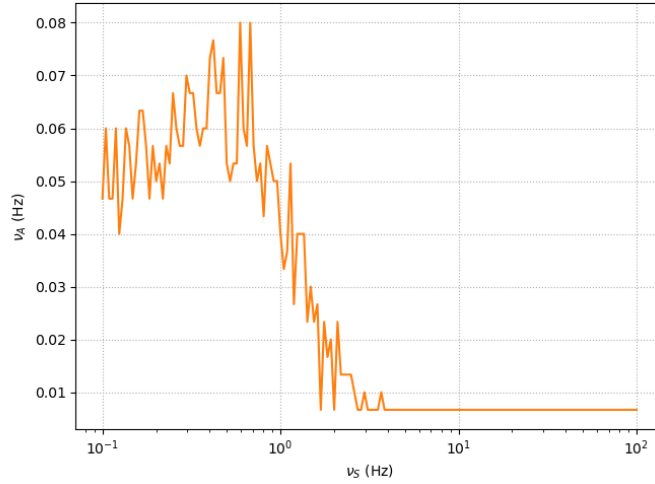


Figure 18: **Numerical estimation of guess function.** (left panel)  $\nu_A(\nu_S)$  with exponential decreasing guess function,  $A = 0.1$  Hz. (right panel) Steady states of neurotransmitter release with respect to presynaptic firing rate.

## Appendix A G-ChI astrocyte model

A corollary of the biological and modeling arguments is that  $\text{Ca}^{2+}$  and  $\text{IP}_3$  signals are, generally speaking, dynamically coupled in astrocytes.

A model that deals with this coupling is the so-called ChI which is constituted by three ODEs, respectively, for intracellular  $\text{Ca}^{2+}$  ( $C$ ), the  $\text{IP}_3$ R gating variable  $h$ , and the mass balance equation for intracellular  $\text{IP}_3$  lumping terms:

$$\begin{aligned}\frac{dC}{dt} &= J_r(C, h, I) + J_l(C) - J_p(C) \\ \frac{dh}{dt} &= \frac{h_\infty(C, I) - h}{\tau_h(C, I)} \\ \frac{dI}{dt} &= J_\delta(C, I) - J_{3K}(C, I) - J_{5P}(I)\end{aligned}\tag{31}$$

The above model can also be extended to include GPCR dynamics by the G-ChI model. To this aim, the contribution of GPCR-mediated  $\text{IP}_3$  synthesis is added to the right-hand side of (31):

$$\begin{aligned}\frac{d\Gamma_A}{dt} &= O_N Y_S (1 - \Gamma_A) - \Omega_N (1 + \zeta \mathcal{H}_1(C, K_{KC})) \Gamma_A \\ \frac{dC}{dt} &= J_r(C, h, I) + J_l(C) - J_p(C) \\ \frac{dh}{dt} &= \frac{h_\infty(C, I) - h}{\tau_h(C, I)} \\ \frac{dI}{dt} &= J_\beta(\Gamma_A) + J_\delta(C, I) - J_{3K}(C, I) - J_{5P}(I)\end{aligned}\tag{32}$$

where  $Y_S$  stands for the neurotransmitter concentration in the periastrorcytic space. The mass balance equation for  $C$  is described by:

$$\begin{aligned}J_p(C) &= O_P \mathcal{H}_2(C, K_P) \\ J_l(C) &= \Omega_L (C_T - (1 + \rho_A)C) \\ J_r(C, h, I) &= \Omega_C m_\infty^3 h_\infty^3 (C_T - (1 + \rho_A)C)\end{aligned}\tag{33}$$

Similary for  $\text{IP}_3$  dynamics:

$$\begin{aligned}J_\beta &= O_\beta \Gamma_A \\ J_\delta &= \Omega_L (C_T - (1 + \rho_A)C) \\ J_{3K} &= O_{3K} \mathcal{H}_4(C, K_D) \mathcal{H}_1(I, K_3) \\ J_{5P} &= \Omega_{5P} I \\ J_\delta &= O_\delta \frac{\kappa_\delta}{\kappa_\delta + I} \mathcal{H}_2(C, K_\delta)\end{aligned}\tag{34}$$

Starting from model (32) it is possible to analyse the dynamical feature of astrocytes. The above results suggests intracellular calcium concentration deeply influences the filtering features of tripartite synapses. An astrocyte defined by parameters in B.2 show a stable fixed points for a wide range of  $Y_S$  values, notably the steady states are always beyond threshold (Figure (19)).

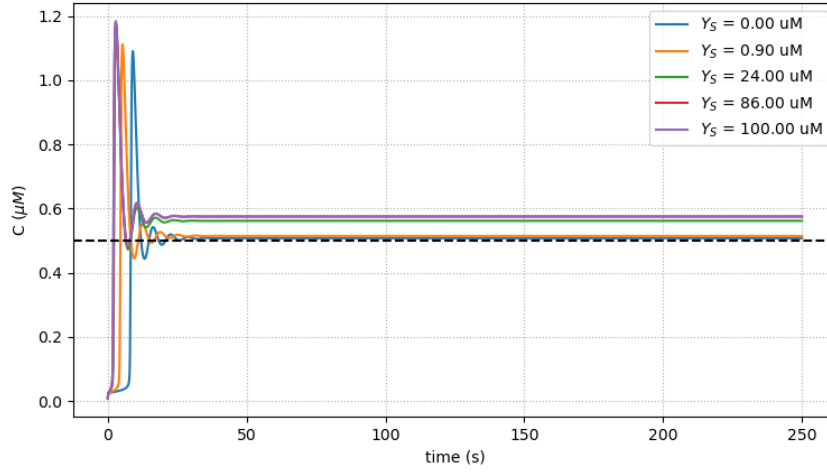


Figure 19: **Astrocyte steady state with respect to extracellular neurotransmitter concentration** . Calcium steady states with 5 different  $Y_S$  values. Simulation runs for 250 seconds with 0.01 seconds of integration time step.

The system goes into the steady state through an initial transient regime where the oscillations depends on initial conditions. Thus, after 50 second, the only possibility for gliotransmitter release is a change of  $Y_S$ .

## Appendix B Model Parameters used in the simulations

The following tables report constants that corresponds to the model parameters used in the simulation.

### B.1 Neurons and synapses

Symbol	Name in code	Value	Units	Description
<i>Neuron parameters</i>				
$C_m$	C_m	198	pF	Membrane capacitance
$E_l$	E_l	-60	mV	Leak reversal potential
$g_l$	g_l	9.99	nS	Leak conductance
$V_r$	V_r	-60	mV	Reset potential
$V_\theta$	V_th	-50	mV	Firing threshold
$\tau_r$	tau_r	5	ms	Refractory period
<i>Synapse parameters</i>				
$\Omega_d$	Omega_d	2	$s^{-1}$	Synaptic depression rate
$\Omega_f$	Omega_f	3.33	$s^{-1}$	Synaptic facilitation rate
$U_0^*$	U_0_star	0.6	-	Resting synaptic release probability
$Y_T$	Y_T	500	mM	Total vesicular neurotransmitter concentration
$\rho_c$	rho_c	0.005	-	Synaptic vesicle-to-extracellular space volume ratio
$\Omega_c$	Omega_c	40	$s^{-1}$	Neurotransmitter clearance rate
$w_e$	w_e	50	pS	Excitatory synaptic conductance
$w_i$	w_i	1	nS	Inhibitory synaptic conductance
$\tau_e$	tau_e	5	ms	Excitatory synaptic time constant
$\tau_i$	tau_i	10	ms	Inhibitory synaptic time constant
$E_e$	E_e	0	mV	Excitatory synaptic reversal potential
$E_i$	E_i	-80	mV	Inhibitory synaptic reversal potential
<i>Presynaptic receptor parameters</i>				
$O_G$	O_G	1.5	$\mu M s^{-1}$	Agonist binding (activating) rate
$\Omega_G$	Omega_G	0.5	$min^{-1}$	Agonist release (deactivating) rate

## B.2 Astrocyte

Symbol	Name in code	Value	Units	Description
<i>Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release</i>				
$C_T$	C_T	2	$\mu\text{M}$	Total cell free Ca <sup>2+</sup> content
$\rho_A$	rho_A	0.18	-	ER-to-cytoplasm volume ratio
$d_1$	d_1	0.13	$\mu\text{M}$	IP <sub>3</sub> binding affinity
$d_2$	d_2	1.05	$\mu\text{M}$	Ca <sup>2+</sup> inactivation dissociation constant
$d_3$	d_3	0.9434	$\mu\text{M}$	IP <sub>3</sub> dissociation constant
$d_5$	d_5	0.08	$\mu\text{M}$	Ca <sup>2+</sup> activation dissociation constant
$O_2$	O_2	0.2	$\mu\text{M s}^{-1}$	IP <sub>3</sub> R binding rate for Ca <sup>2+</sup> inhibition
$\Omega_C$	Omega_C	6	$\text{s}^{-1}$	Maximal rate of Ca <sup>2+</sup> release by IP <sub>3</sub> Rs
$\Omega_L$	Omega_L	0.1	$\text{s}^{-1}$	Maximal rate of Ca <sup>2+</sup> leak from the ER
$O_P$	O_P	0.9	$\mu\text{M s}^{-1}$	Maximal Ca <sup>2+</sup> uptake rate by SERCAs
$K_P$	K_P	0.05	$\mu\text{M}$	Ca <sup>2+</sup> affinity of SERCAs
<i>IP<sub>3</sub> signaling</i>				
$O_\beta$	O_beta	0.5	$\mu\text{M s}^{-1}$	Maximal rate of IP <sub>3</sub> production by PLC $\beta$
$O_\delta$	O_delta	1.2	$\mu\text{M s}^{-1}$	Maximal rate of IP <sub>3</sub> production by PLC $\delta$
$\kappa_\delta$	kapppa_delta	1.5	$\mu\text{M}$	Inhibition constant of PLC $\delta$ by IP <sub>3</sub>
$K_\delta$	K_delta	0.1	$\mu\text{M}$	Ca <sup>2+</sup> affinity of PLC $\delta$
$O_{3K}$	O_3K	4.5	$\mu\text{M s}^{-1}$	Maximum rate of IP <sub>3</sub> degradation by IP <sub>3</sub> -3K
$K_{3K}$	K_3K	1.0	$\mu\text{M}$	IP <sub>3</sub> affinity of IP <sub>3</sub> -3K
$K_D$	K_D	0.7	$\mu\text{M}$	Ca <sup>2+</sup> affinity of IP <sub>3</sub> -3K
$\Omega_{5P}$	Omega_5P	0.05	$\text{s}^{-1}$	Maximal rate of IP <sub>3</sub> degradation by IP-5P
<i>Metabotropic receptor kinetics</i>				
$O_N$	O_N	0.3	$\mu\text{M s}^{-1}$	Agonist binding rate
$\Omega_N$	Omega_N	0.5	$\text{s}^{-1}$	Maximal inactivation rate
$K_{KC}$	K_KC	0.5	$\mu\text{M}$	Ca <sup>2+</sup> affinity of PKC
$\zeta$	zeta	10	-	Maximal reduction of receptor affinity by PKC
<i>Gliotrasmission</i>				
$C_\theta$	C_theta	0.5	$\mu\text{M}$	Ca <sup>2+</sup> threshold for exocytosis
$G_T$	G_T	200	mM	Total vesicular gliotransmitter concentration
$\Omega_A$	Omega_A	0.6	$\text{s}^{-1}$	Gliotransmitter recycling rate
$U_A$	U_A	0.6	-	Gliotransmitter release probability
$\rho_e$	rho_e	$6.5 \cdot 10^{-4}$	-	Astrocytic vesicle-to-extracellular volume ratio
$\Omega_e$	Omega_e	60	$\text{s}^{-1}$	Gliotransmitter clearance rate
$\alpha$	alpha	0	-	Gliotrasmission nature

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