S1 Appendix

Astrocyte-mediated spike-timing-dependent long-term depression modulates synaptic properties in the developing cortex

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To study the role of astrocytes in modulation of spike-timing-dependent long-term depression (t-LTD) in somatosensory cortex, we simulated a layer 4 (L4) to layer 2/3 (L2/3) synapse model. In the model, we described major biophysical and biochemical mechanisms for the one-compartmental presynaptic L4 spiny stellate cell, two-compartmental (soma and dendrite) postsynaptic L2/3 pyramidal cell, and one-compartmental nearby fine astrocyte process. We chose to include the most important signaling pathways that were assumed to be crucial in explaining t-LTD at L4-L2/3 synapse. We stimulated our synapse model using t-LTD stimulation protocols with a varying temporal difference between post- and presynaptic activity.

The model components are shortly the following:

- **Presynaptic neuron model**
  - High-voltage-activated (HVA) N-type calcium (Ca$^{2+}$) (Ca$_{\text{NHVA}}$) channel
  - Potassium (K$^+$) channel
  - Sodium (Na$^+$) channel
  - Leak channel
  - N-methyl-D-aspartate receptor (NMDAR) composed of GluN1 and either GluN2C or GluN2D subunits (GluN2C/D-containing NMDAR)
  - Calcineurin (CaN) signaling
  - CaN-dependence to available glutamate (Glu) release
  - Glu release model modified from

- **Postsynaptic neuron model**
  - L-type HVA Ca$^{2+}$ (Ca$_{\text{LHVA}}$) channel
  - Low-voltage-activated (LVA) L-type Ca$^{2+}$ (Ca$_{\text{LLVA}}$) channel
  - A-type K$^+$ (K$_A$) channel
  - Delayed rectifier K$^+$ (K$_{\text{DR}}$) channel
  - Na$^+$ channel
  - Persistent Na$^+$ (Na$_P$) channel
  - Leak channel
  - Coupling currents
- α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) [16]
- NMDAR composed of GluN1 and GluN2B subunits (GluN2B-containing NMDAR) [16]
- Metabotropic Glu receptor (mGluR) [17]
- Inositol 1,4,5-trisphosphate (IP₃) receptor (IP₃R) [18–20]
- Plasma membrane Ca²⁺-ATPase (PMCA pump) [21]
- Sarco/endoplasmic reticulum (ER) Ca²⁺-ATPase (SERCA pump) [18,19]
- Leak flux [18,19]
- Ca²⁺ buffer [22]
- Reactions from mGluR activation to 2-arachidonoylglycerol (2-AG) release [17,22]

• Astrocyte model
- IP₃ activation by postsynaptic 2-AG modified from [23]
- IP₃R [18,19]
- SERCA pump [18,19]
- Leak flux [18,19]
- Glu release model [6–10]

Stimulation Protocols and Simulation Results

The following stimulation protocols were used [24]:

1. The stimulation protocol before t-LTD induction consisted of five 10 ms long presynaptic stimuli at a frequency of 0.2 Hz and with an amplitude of 10 µA/cm² keeping the fraction of presynaptic Glu release inhibition (fₚₑᵣₑ) as constant zero.

2. The t-LTD induction protocol consisted of a 10 ms long postsynaptic stimulus with an amplitude of 25 µA/cm² occurring between 10 ms and 200 ms before a 10 ms long presynaptic stimulus with an amplitude of 10 µA/cm² and the post-pre pairing was repeated 100 times at a frequency of 0.2 Hz. Thus, the temporal difference (ΔT) between the pre- and postsynaptic stimulus in this study had negative values meaning that the postsynaptic stimulus occurred before the presynaptic stimulus: ΔT had values between –10 ms and –200 ms. Note that in simulations ΔT values were implemented as positive because we set the postsynaptic stimuli to occur at fixed time points in all the simulations whereas the presynaptic stimuli occurred in varying time points after the postsynaptic stimuli depending on ΔT, and not the other way around. The initial value of fₚₑᵣₑ in these simulations was zero, but it increased during the stimulation protocol to above zero depending on ΔT used in the t-LTD induction protocol.

3. The stimulation protocol after t-LTD induction consisted of five 10 ms long presynaptic stimuli at a frequency of 0.2 Hz and with an amplitude of 10 µA/cm² keeping fₚₑᵣₑ as constant value received from the t-LTD induction protocol. For the fraction fₚₑᵣₑ, we used the final simulation value received from the simulation with the t-LTD induction protocol. Thus, fₚₑᵣₑ had different constant values depending on ΔT used in the t-LTD induction protocol.
Computational Model

The used abbreviations can be found in Table A. The values used throughout the synapse model for certain parameters are given in Table B.

Presynaptic neuron model

We extended a previously published presynaptic one-compartmental neuron model [2] by adding (1) CaNHVA channels [1], (2) GluN2C/D-containing NMDARs [3,4], (3) Ca\(^{2+}\) signaling [1], (4) CaN signaling [5], (5) CaN-dependence to available Glu release, and (6) Glu release to the synaptic cleft (modified from [6–10]).

The differential equation for the presynaptic membrane potential can be given as [2]

\[
C_{m,pre} \frac{dV_{pre}}{dt} = -I_{CaNHVA,pre} - I_{K,pre} - I_{Na,pre} - I_{L,pre} - I_{Ca,NMDAR,pre} - I_{Na,NMDAR,pre} + I_{ext,pre},
\]

where \(C_{m,pre}\) is the presynaptic membrane capacitance per unit area, \(I_{CaNHVA,pre}\) is the current density via CaNHVA channels, \(I_{K,pre}\) is the K\(^+\) current density, \(I_{Na,pre}\) is the Na\(^+\) current density, \(I_{L,pre}\) is the leak current density, \(I_{Ca,NMDAR,pre}\) and \(I_{Na,NMDAR,pre}\) are the Ca\(^{2+}\) and Na\(^+\) current densities via NMDARs, and \(I_{ext,pre}\) is the stimulus current injected into the presynaptic neuron per unit area. The channels presented in Eq (1) are described by the Hodgkin-Huxley and Goldman-Hodgkin-Katz formalisms [1,2]. The differential equations for the gating variables \(x\) (\(m_{CaNHVA,pre}\), \(h_{CaNHVA,pre}\), \(n_{K,pre}\), \(n_{K,2,pre}\), \(m_{Na,pre}\), and \(h_{Na,pre}\)) of different currents presented in Eq (1) can be given as [1,2]

\[
\frac{dx}{dt} = \frac{x_{\infty} - x}{\tau_x},
\]

where \(x_{\infty}\) and \(\tau_x\) denote the steady-state values and time constants for different gating variables, respectively. For the gating variable \(s_{Na,pre}\), the differential equation is [2]

\[
\frac{ds_{Na,pre}}{dt} = \frac{s_{\infty,Na,pre} - s_{Na,pre}}{\tau_{s,Na,pre}\sigma_{s,Na,pre} + \tau_{sh,Na,pre}},
\]

where \(s_{\infty,Na,pre}\) denotes the steady-state value, \(\tau_{s,Na,pre}\) and \(\tau_{sh,Na,pre}\) denote the time constants, and \(\sigma_{s,Na,pre}\) denotes a shift in the time constant.

Presynaptic Ca\(^{2+}\) concentrations are increased by Ca\(^{2+}\) influxes through presynaptic NMDARs and CaNHVA channels. The NMDAR-mediated Ca\(^{2+}\) concentration activates CaN, and then CaN inhibits vesicle exocytosis and Glu release from the presynaptic neuron [25,26]. The concentration of Ca\(^{2+}\) mediated by CaNHVA channels activates vesicle exocytosis and Glu release from the presynaptic neuron. The differential equation for the presynaptic Ca\(^{2+}\) concentration through CaNHVA channels is [27]

\[
\frac{d[Ca^{2+}]_{CaNHVA,pre}}{dt} = - \frac{I_{CaNHVA,pre}}{c_{Ca,pre}} + \frac{Ca_{rest,pre} - [Ca^{2+}]_{CaNHVA,pre}}{\tau_{Ca,pre}},
\]

and the differential equation for the presynaptic Ca\(^{2+}\) concentration mediated by NMDARs is [27]

\[
\frac{d[Ca^{2+}]_{NMDAR,pre}}{dt} = - \frac{I_{Ca,NMDAR,pre}}{c_{Ca,pre}} + \frac{Ca_{rest,pre} - [Ca^{2+}]_{NMDAR,pre}}{\tau_{Ca,pre}},
\]

where \(c_{Ca,pre}\), \(Ca_{rest,pre}\), and \(\tau_{Ca,pre}\) are the presynaptic scaling factor to convert from units \(\mu\text{A} / \text{cm}^2\) to \(\mu\text{M} / \text{ms}\), presynaptic resting Ca\(^{2+}\) concentration, and time constant of a
presynaptic pump, respectively. The presynaptic pump takes into account the effect of SERCA and PMCA pumps as well as Na⁺/Ca²⁺ exchangers [27].

The presynaptic NMDAR-mediated Ca²⁺ influx presented in Eq (5) activates presynaptic CaN [26], and the differential equation for the presynaptic CaN concentration can be given as [7]

$$\frac{d[\text{CaN}]_{\text{pre}}}{dt} = k_{1,\text{pre}} \left( \text{CaN}_{\text{max,pre}} - [\text{CaN}]_{\text{pre}} \right) \left[ \text{Ca}^{2+} \right]_{\text{NMDAR,pre}}^3 - k_{2,\text{pre}}[\text{CaN}]_{\text{pre}} \ , \ (6)$$

where $k_{1,\text{pre}}$ and $k_{2,\text{pre}}$ are the rate constants for the activation and inactivation of presynaptic CaN, respectively, and $\text{CaN}_{\text{max,pre}}$ is the total concentration of presynaptic CaN. Calcineurin has been shown to regulate a specific phase of synaptic vesicle cycling, thus influencing the vesicle release [28–31]. We modeled the effect of CaN to Glu release via a signaling pathway linking CaN to vesicle release and recycling in the presynaptic terminal with the following differential equation

$$\frac{d[X]_{\text{jac,pre}}}{dt} = p_{1,\text{pre}} \frac{[\text{CaN}]_{z,\text{pre}}}{K_{A,\text{pre}} + [\text{CaN}]_{z,\text{pre}}} \left( X_{\text{total,pre}} - [X]_{\text{jac,pre}} \right) \ , \ (7)$$

where $[X]_{\text{jac,pre}}$ is the active concentration and $X_{\text{total,pre}}$ is the total concentration of the unspecified protein that affects the vesicle release, $p_{1,\text{pre}}$ is the rate constant, $K_{A,\text{pre}}$ is the CaN concentration producing half occupation, and $n_{2,\text{pre}}$ is the Hill coefficient.

The differential equation for the fraction of releasable presynaptic vesicles is [7][10]

$$\frac{dR_{\text{rel,pre}}}{dt} = k_{\text{recov,pre}} (1 - R_{\text{rel,pre}}) - \sum_j P_{\text{rel,pre}} R_{\text{rel,pre}} \delta(t - t_j) \ \ (8)$$

and the differential equation for the release probability of presynaptic Glu vesicles was combined and modified from previously published equations [7][10] and is given as

$$\frac{dP_{\text{rel,pre}}}{dt} = -k_{t,\text{pre}} P_{\text{rel,pre}}$$

$$+ \sum_j (1 - f_{\text{pre}}) \frac{[\text{Ca}^{2+}]_{\text{CaNHVA,pre}}^{n_{1,\text{pre}}}}{K_{\text{rel,pre}}^{n_{1,\text{pre}}} + [\text{Ca}^{2+}]_{\text{CaNHVA,pre}}^{n_{1,\text{pre}}}} (1 - P_{\text{rel,pre}}) \delta(t - t_j) \ , \ (9)$$

where the fraction ($f_{\text{pre}}$), which is the active concentration ($[X]_{\text{jac,pre}}$) divided by the total concentration ($X_{\text{total,pre}}$) of the protein, affects the probability of presynaptic Glu release. Note that $f_{\text{pre}}$ inhibits $P_{\text{rel,pre}}$ and excites $R_{\text{rel,pre}}$. Parameters $k_{\text{recov,pre}}, k_{t,\text{pre}}, K_{\text{rel,pre}},$ and $n_{1,\text{pre}}$ describe the presynaptic recovery rate constant from empty to releasable state, facilitation rate constant, Ca²⁺ concentration producing half occupation used in calculation of Glu release, and Hill coefficient, respectively. The differential equation for the Glu concentration in the synaptic cleft was combined and modified from previously published Glu equations [8][10] and Glu-activated postsynaptic equations related to mGluRs [17] and is given as

$$\frac{d[\text{Glu}]_{\text{syncleft}}}{dt} = -v_{\text{Glu,f,post}} - v_{\text{mGluR,f,post}} + v_{\text{mGluR,b,post}}$$

$$+ \sum_j \frac{G_{\text{pre}} N_{\text{pre}} P_{\text{rel,pre}} R_{\text{rel,pre}}}{k_{\text{Glu,pre}} N_A V_{\text{syncleft}}} \delta(t - t_j) \ , \ (10)$$

where $v_{\text{Glu,f,post}}, v_{\text{mGluR,f,post}},$ and $v_{\text{mGluR,b,post}}$ are the reaction rates for the postsynaptic mGluR Glu uptake, and postsynaptic mGluR Glu binding and unbinding, respectively. Parameters $G_{\text{pre}}, N_{\text{pre}}, k_{\text{Glu,pre}}, N_A,$ and $V_{\text{syncleft}}$ denote the number of
Glu per presynaptic vesicle, number of readily releasable presynaptic vesicles, scaling factor to convert from units $M$ to $\mu M$, Avogadro’s constant, and volume of synaptic cleft, respectively. In Eq (8)–(10), the presynaptic Glu release occurs at the first time point $t = t_j$ such that $[\text{Ca}^{2+}]_{\text{pre}} \geq C_{\text{thr,pre}}$ and less than 10 ms has passed from the previous presynaptic membrane potential crossing 0 mV from negative to positive voltages ($V_{\text{pre}} \geq 0$, $\frac{dV_{\text{pre}}}{dt} > 0$) at that time point $t_j$. The $\delta$ function has units of $\frac{1}{\text{ms}}$.

Experimental studies have reported that presynaptic GluN2C/D-containing NMDARs are required for t-LTD at L4 to L2/3 synapses 24,32–37, whereas postsynaptic GluN2B-containing NMDARs are necessary for spike-timing-dependent long-term potentiation (t-LTP) at L4-L2/3 and L2/3-L2/3 synapses, and postsynaptic GluN2A-containing NMDARs are required in t-LTD at L2/3-L2/3 synapses 24,32,37. Thus, we modeled presynaptic GluN2C/D-containing NMDARs 3,4. The closed presynaptic NMDAR (represented in Eq (11) as fraction $R_{\text{pre}}$) binds two agonists (represented in equations as A), such as Glu, and yields to $R_{A_{2,\text{pre}}}$.

In our synapse model, presynaptic NMDARs are activated by the sum of available Glu in the synaptic cleft and extrasynaptic space, where the Glu concentration in the synaptic cleft is multiplied by a parameter $f_{\text{Glur,pre}}$ to denote the effect of spillover of glutamate from the synaptic cleft to the extrasynaptic space and that not all Glu in the synaptic cleft activates presynaptic NMDARs (most part of Glu in the synaptic cleft activates the postsynaptic receptors). The differential equations for these variables are 3,4

$$\frac{dR_{\text{pre}}}{dt} = -v_{\text{kon,pre}} + v_{\text{koff,pre}} , \tag{11}$$

$$\frac{dR_{A_{\text{pre}}}}{dt} = v_{\text{kon,pre}} - v_{\text{koff,pre}} - v_{\text{kon,pre}} + 2v_{\text{koff,pre}} , \tag{12}$$

and

$$\frac{dR_{A_{2,\text{pre}}}}{dt} = v_{\text{kon,pre}} - v_{\text{koff,pre}} - v_{d1,f,\text{pre}} - v_{d1,b,\text{pre}} - v_{d2,f,\text{pre}} + v_{d2,b,\text{pre}} + v_{t1,f,\text{pre}} + v_{t1,b,\text{pre}} + v_{s1,f,\text{pre}} + v_{s1,b,\text{pre}} . \tag{13}$$

Glutamate available for the presynaptic NMDARs is present in some of the reaction rates in Eq (11)–(13).

Then $R_{A_{2,\text{pre}}}$ form of the NMDARs in Eq (13) can either become one of the two desensitized states (represented in Eq (14) as $R_{A_{2,d1,\text{pre}}}$ or in Eq (15) as $R_{A_{2,d2,\text{pre}}}$), or go through a faster conformational change of the GluN1 subunit of the NMDAR (represented in Eq (16) as $R_{A_{2,t,\text{pre}}}$) or a slower conformational change of the GluN2 subunit of the NMDAR (represented in Eq (17) as $R_{A_{2,s,\text{pre}}}$). The differential equations for these variables are 3,4

$$\frac{dR_{A_{2,d1,\text{pre}}}}{dt} = v_{d1,f,\text{pre}} - v_{d1,b,\text{pre}} , \tag{14}$$

$$\frac{dR_{A_{2,d2,\text{pre}}}}{dt} = v_{d2,f,\text{pre}} - v_{d2,b,\text{pre}} , \tag{15}$$

$$\frac{dR_{A_{2,t,\text{pre}}}}{dt} = v_{t1,f,\text{pre}} - v_{t1,b,\text{pre}} - v_{s2,f,\text{pre}} + v_{s2,b,\text{pre}} , \tag{16}$$

and

$$\frac{dR_{A_{2,s,\text{pre}}}}{dt} = v_{s1,f,\text{pre}} - v_{s1,b,\text{pre}} - v_{t2,f,\text{pre}} + v_{t2,b,\text{pre}} . \tag{17}$$

The slow and fast components can proceed towards magnesium (Mg$^{2+}$)-unblocked (open) NMDAR state and the differential equation for it can be given as 3,4

$$\frac{dR_{A_{2,0,\text{pre}}}}{dt} = v_{s2,f,\text{pre}} - v_{s2,b,\text{pre}} + v_{t2,f,\text{pre}} - v_{t2,b,\text{pre}} - v_{\text{Mg,f,pre}} + v_{\text{Mg,b,pre}} . \tag{18}$$
Similarly to Eq [11]–[18], NMDAR equations with Mg$^{2+}$ blocking can be given as [4]

\[
\frac{dR_{A,\text{pre}}}{dt} = v_{2\text{konMg,pre}} - v_{\text{konMg,pre}} - v_{\text{d1Mg,f,pre}} + v_{\text{d1Mg,b,pre}} - v_{\text{d2Mg,pre}} + v_{\text{d2Mg,b,pre}},
\]

(19)

\[
\frac{dR_{A,\text{f,pre}}}{dt} = v_{2\text{konMg,pre}} - v_{\text{konMg,pre}} - v_{\text{d1Mg,f,pre}} + v_{\text{d1Mg,b,pre}} - v_{\text{d2Mg,pre}} + v_{\text{d2Mg,b,pre}},
\]

(20)

\[
\frac{dI_{A,\text{pre}}}{dt} = v_{2\text{konMg,pre}} - v_{\text{konMg,pre}} - v_{\text{d1Mg,f,pre}} + v_{\text{d1Mg,b,pre}} - v_{\text{d2Mg,pre}} + v_{\text{d2Mg,b,pre}},
\]

(21)

\[
\frac{dR_{A,\text{d1,pre}}}{dt} = v_{\text{d1Mg,f,pre}} - v_{\text{d1Mg,b,pre}},
\]

(22)

\[
\frac{dR_{A,\text{d2,pre}}}{dt} = v_{\text{d2Mg,f,pre}} - v_{\text{d2Mg,b,pre}},
\]

(23)

\[
\frac{dR_{A,\text{f,pre}}}{dt} = v_{\text{f1Mg,f,pre}} - v_{\text{f1Mg,b,pre}} - v_{\text{s1Mg,f,pre}} + v_{\text{s1Mg,b,pre}} - v_{\text{s2Mg,pre}} + v_{\text{s2Mg,b,pre}},
\]

(24)

\[
\frac{dR_{A,\text{d1,pre}}}{dt} = v_{\text{s1Mg,f,pre}} - v_{\text{s1Mg,b,pre}} - v_{\text{s2Mg,f,pre}} + v_{\text{s2Mg,b,pre}},
\]

(25)

\[
\frac{dR_{A,\text{d2,pre}}}{dt} = -v_{2\text{Mg,f,pre}} - v_{2\text{Mg,b,pre}} + v_{\text{f2Mg,f,pre}} - v_{\text{f2Mg,b,pre}} + v_{\text{f1Mg,f,pre}} - v_{\text{f1Mg,b,pre}} - v_{\text{s1Mg,f,pre}} + v_{\text{s1Mg,b,pre}} - v_{\text{s2Mg,pre}} + v_{\text{s2Mg,b,pre}},
\]

and, finally, the Mg$^{2+}$-blocked NMDAR state can be given as [4]

\[
\frac{dR_{A,\text{O,pre}}}{dt} = v_{2\text{Mg,f,pre}} - v_{2\text{Mg,b,pre}} + v_{\text{f2Mg,f,pre}} - v_{\text{f2Mg,b,pre}} - v_{\text{f1Mg,f,pre}} + v_{\text{f1Mg,b,pre}} - v_{\text{s1Mg,f,pre}} + v_{\text{s1Mg,b,pre}} - v_{\text{s2Mg,pre}} + v_{\text{s2Mg,b,pre}}.
\]

(26)

The intermediate variables needed to solve Eq [1]–[26] can be found in Tables C–J and F. The list of presynaptic reactions can be found in Table E. The parameter values of the presynaptic model can be found in Tables C–J and initial values in Table K.

**Postsynaptic neuron model**

We modified a previously published postsynaptic two-compartmental neuron model [15] by adopting (1) $K_A$, $K_{DR}$, Na$^+$, and NaP channels [14], (2) Ca$_{\text{LHVA}}$ channels [11,12], (3) Ca$_{\text{LVA}}$ channels [13], (4) AMPARs [16], (5) GluN2B-containing NMDARs [16], (6) mGluR activation to endocannabinoid 2-AG release [17,22], and (7) Ca$^{2+}$ signaling [18,19,21,22].

The postsynaptic neuron model for the two compartments, a soma and a dendrite, was modified from a previously published study [15]. The differential equations for the membrane potentials of these two compartments are

\[
C_{m,\text{post}} \frac{dV_{\text{soma,post}}}{dt} = -I_{K_{DR,\text{soma,post}}} - I_{Na,\text{soma,post}} - I_{NaP,\text{soma,post}} - I_{L,\text{soma,post}} + I_{\text{coupl,soma,post}} + I_{\text{ext,post}}
\]

(27)

and

\[
C_{m,\text{post}} \frac{dV_{\text{dend,post}}}{dt} = -I_{K_A,\text{dend,post}} - I_{Ca_{\text{LHVA}},\text{dend,post}} - I_{Ca_{\text{LVA}},\text{dend,post}} - I_{Na,\text{dend,post}} - I_{L,\text{dend,post}} - I_{\text{AMPAR,post}} - I_{Ca,\text{NMDAR,post}} + I_{\text{coupl,dend,post}}
\]

(28)

where $C_{m,\text{post}}$ is the membrane capacitance per unit area, $I_{K_{DR,\text{soma,post}}}$ is the somatic $K_{DR}$ current density, $I_{Na,\text{soma,post}}$ and $I_{Na,\text{dend,post}}$ are the somatic and dendritic Na$^+$
current densities, $I_{NaP,soma,post}$ is the somatic $NaP$ current density, $I_{L,soma,post}$ and $I_{L,dend,post}$ are the somatic and dendritic leak current densities, $I_{coupl,soma,post}$ and $I_{coupl,dend,post}$ are the somatic and dendritic coupling terms, $I_{ext,post}$ is the current injected into the soma per unit area, $I_{Ka,dend,post}$ is the dendritic $K_A$ current density, $I_{CaLHVA,dend,post}$ and $I_{CaLLVA,dend,post}$ are the dendritic $Ca_{LHVA}$ and $Ca_{LLVA}$ current densities, and $I_{AMPAR,post}$ and $I_{NMDAR,post}$ are the synaptic current densities via AMPARs and NMDARs in the dendrite. We used Hodgkin-Huxley formalism to describe the behavior of ionic currents [11][14].

The differential equations for the fractions of postsynaptic AMPARs and GluN2B-containing NMDARs in open state can be modified from a previously published study [16] and given as

$$\frac{dm_{AMPAR,post}}{dt} = \alpha_{AMPAR,post}(1 - f_{Glu,pre})[Glu]_{syncleft}(1 - m_{AMPAR,post}) - \beta_{AMPAR,post}m_{AMPAR,post}$$

and

$$\frac{dm_{NMDAR,post}}{dt} = \alpha_{NMDAR,post}(1 - f_{Glu,pre})[Glu]_{syncleft}(1 - m_{NMDAR,post}) - \beta_{NMDAR,post}m_{NMDAR,post},$$

where $\alpha_{AMPAR,post}$ and $\beta_{AMPAR,post}$ describe the rate constants of opening and closing postsynaptic AMPARs, respectively, and similarly to NMDARs. Parameter $1 - f_{Glu,pre}$ denotes the part of Glu in synaptic cleft that activates the postsynaptic receptors. Other differential equations for the gating variables $x$ ($m_{KDR,soma,post}$, $m_{Na,soma,post}$, $m_{CaLHVA,dend,post}$, $h_{CaLHVA,dend,post}$, $m_{CaLLVA,dend,post}$, $h_{CaLLVA,dend,post}$, $m_{Ka,dend,post}$, $h_{Ka,dend,post}$, $m_{Na,dend,post}$, and $h_{Na,dend,post}$) of different currents presented in Eq (27) and (28) and for the IP$_3$R inactivation gating variable ($h_{IP3R,post}$) can be given as [11][14][18][19]

$$\frac{dx}{dt} = \frac{x_\infty - x}{\tau_x},$$

where $x_\infty$ and $\tau_x$ denote the steady-state values and time constants for different gating variables, respectively.

The biochemical mechanisms related to mGluRs and the activation of the $G$-protein signaling cascade, as well as the subsequent production of endocannabinoids are included in the synapse model to study the effect of endocannabinoids on the nearby astrocyte. Next, we present the differential equations starting from the mGluR activation to the endocannabinoid 2-AG release [17][22].

Glutamate in the synaptic cleft activates postsynaptic mGluRs and induces dissociation of the $G$ protein $\alpha$ subunit bound with guanosine-5'-triphosphate (GzGTP) from the mGluR-bound $G$ protein with $\beta$ and $\gamma$ subunits ($G_{\beta\gamma}$). The differential equation for the concentration of the postsynaptic mGluRs is [17]

$$\frac{d[m\text{GluR}]_{post}}{dt} = -v_{m\text{GluR},f,post} + v_{m\text{GluR},b,post},$$

for the concentration of the Glu-mGluR complex is [17]

$$\frac{d[\text{Glu}-m\text{GluR}]_{post}}{dt} = v_{m\text{GluR},f,post} - v_{m\text{GluR},b,post} - v_{m\text{GluRdes},f,post} + v_{m\text{GluRdes},b,post} - v_{Gact,f,post} + v_{Gact,b,post} + v_{Gact,c,post}.$$
and for the concentration of the desensitized Glu-mGluR complex is \[17\]

\[
\frac{d[Glu\_mGluR\_desens]_{post}}{dt} = v_{mGluRdes,f,post} - v_{mGluRdes,b,post}. \tag{34}
\]

The differential equation for the concentration of G protein with $\alpha$, $\beta$, and $\gamma$ subunits (G$\alpha\beta\gamma$) is \[17\]

\[
\frac{d[G\alpha\beta\gamma]_{post}}{dt} = -v_{Gact,f,post} + v_{Gact,b,post} + v_{regen,G,f,post}.
\tag{35}
\]

and for G$\alpha\beta\gamma$ bound with Glu and mGluRs is \[17\]

\[
\frac{d[G\alpha\beta\gamma\_Glu\_mGluR]_{post}}{dt} = v_{Gact,f,post} - v_{Gact,b,post} - v_{Gact,c,post}.
\tag{36}
\]

The differential equation for the concentration of G$\alpha$GTP can be given as \[17\]

\[
\frac{d[G\alpha\GTP]_{post}}{dt} = v_{Gact,c,post} - v_{G\_PLC2,f,post} + v_{G\_PLC2,b,post}
+ v_{Ca\_PLC1,b,post} - v_{DAG1,f,post} + v_{DAG1,b,post}
+ J_{IP3R,post} - J_{SERCA,post} + J_{leakER,post} + J_{CaL,post}
+ J_{NMDAR,post} - J_{PMCA,post} + J_{leakCell,post}.
\tag{37}
\]

Calcium binds to phospholipase C (PLC), and G$\alpha$GTP can enhance its activity. The differential equation for the concentration of postsynaptic Ca$^{2+}$ is \[17\] \[19\] \[21\]

\[
\frac{d[Ca^{2+}]_{post}}{dt} = -v_{Ca\_PLC1,f,post} + v_{Ca\_PLC1,b,post} - v_{Ca\_PLC2,f,post}
+ v_{Ca\_PLC2,b,post} - v_{DAG1,f,post} + v_{DAG1,b,post}
+ J_{IP3R,post} - J_{SERCA,post} + J_{leakER,post} + J_{CaL,post}
+ J_{NMDAR,post} - J_{PMCA,post} + J_{leakCell,post}.
\tag{38}
\]

and for the concentration of Ca$^{2+}$ in the ER is \[18\] \[19\] \[21\]

\[
\frac{d[Ca^{2+}]_{ER,post}}{dt} = -J_{IP3R,post} + J_{SERCA,post} - J_{leakER,post}
\frac{1}{r_{ER,cyt,post}},
\tag{39}
\]

where $J_{IP3R,post}$ is the Ca$^{2+}$ flux via IP$3$Rs from the ER into the cytosol, $J_{SERCA,post}$ is the Ca$^{2+}$ flux via SERCA pumps from the cytosol into the ER, $J_{leakER,post}$ is the Ca$^{2+}$ leak flux from the ER into the cytosol, $J_{CaL,post}$ is the combined flux via Ca$\_L$VHA and Ca$\_L$VA channels, $J_{NMDAR,post}$ is the Ca$^{2+}$ flux via NMDARs, $J_{PMCA,post}$ is the Ca$^{2+}$ flux via PMCA pumps, and $J_{leakcell,post}$ is the leak flux from the extracellular space to the cytosol. Parameter $r_{ER,cyt,post}$ denotes the ratio between postsynaptic ER and cytosol volumes. The differential equation for the concentration of PLC can be given as \[17\]

\[
\frac{d[PLC]_{post}}{dt} = -v_{Ca\_PLC1,f,post} + v_{Ca\_PLC1,b,post} - v_{G\_PLC1,f,post}
+ v_{G\_PLC1,b,post} + v_{GAP1,f,post}.
\tag{40}
\]

and for the concentration of the Ca$^{2+}$-PLC complex can be given as \[17\]

\[
\frac{d[Ca\_PLC]_{post}}{dt} = v_{Ca\_PLC1,f,post} - v_{Ca\_PLC1,b,post} - v_{G\_PLC2,f,post}
+ v_{G\_PLC2,b,post} - v_{DAG1,f,post} + v_{DAG1,b,post}
+ v_{DAG2,f,post} + v_{GAP2,f,post}.
\tag{41}
\]
The differential equation for the concentration of the Ca\(^{2+}\)-G\(\alpha\)GTP-PLC complex is \(17\)

\[
\frac{d[CaG\alpha GTP_{PLC}]_{\text{post}}}{dt} = v_{G\text{PLC}2,f,\text{post}} - v_{G\text{PLC}2,b,\text{post}} + v_{Ca\text{PLC}2,f,\text{post}} - v_{Ca\text{PLC}2,b,\text{post}} - v_{DAG3,f,\text{post}} + v_{DAG3,b,\text{post}} + v_{DAG4,f,\text{post}} - v_{GAP2,f,\text{post}} \tag{42}
\]

and for the concentration of the G\(\alpha\)GTP-PLC complex is \(17\)

\[
\frac{d[G\alpha GTP_{PLC}]_{\text{post}}}{dt} = v_{G\text{PLC}1,f,\text{post}} - v_{G\text{PLC}1,b,\text{post}} - v_{Ca\text{PLC}2,f,\text{post}} + v_{Ca\text{PLC}2,b,\text{post}} - v_{GAP1,f,\text{post}} + v_{GAP1,b,\text{post}} \tag{43}
\]

Active PLC can then produce IP\(_3\) and diacylglycerol (DAG) from phosphatidylinositol 4,5-bisphosphate (PIP\(_2\)). The differential equation for the concentration of PIP\(_2\) is \(17\)

\[
\frac{d[PIP2]_{\text{post}}}{dt} = -v_{DAG1,f,\text{post}} + v_{DAG1,b,\text{post}} - v_{DAG3,f,\text{post}} + v_{DAG3,b,\text{post}} + v_{PIP2,c,\text{post}} \tag{44}
\]

for the concentration of the Ca\(^{2+}\)-PIP\(_2\)-PLC complex is \(17\)

\[
\frac{d[CaPIP2_{PLC}]_{\text{post}}}{dt} = v_{DAG3,f,\text{post}} - v_{DAG3,b,\text{post}} - v_{DAG3,c,\text{post}} \tag{45}
\]

and for the concentration of the Ca\(^{2+}\)-DAG-PLC complex is \(17\)

\[
\frac{d[CaDAG_{PLC}]_{\text{post}}}{dt} = v_{DAG1,c,\text{post}} - v_{DAG2,f,\text{post}} \tag{46}
\]

The differential equation for the concentration of the Ca\(^{2+}\)-G\(\alpha\)GTP-PIP\(_2\)-PLC complex is \(17\)

\[
\frac{d[CaG\alpha GTP_{PIP2_{PLC}}]_{\text{post}}}{dt} = v_{DAG3,f,\text{post}} - v_{DAG3,b,\text{post}} - v_{DAG3,c,\text{post}} \tag{47}
\]

and for the concentration of the Ca\(^{2+}\)-DAG-G\(\alpha\)GTP-PLC complex is \(17\)

\[
\frac{d[CaDAG_{G\alpha GTP_{PLC}}]_{\text{post}}}{dt} = v_{DAG3,c,\text{post}} - v_{DAG4,f,\text{post}} \tag{48}
\]

The differential equation for the concentration of the G protein with \(\alpha\) subunit bound with guanosine diphosphate (G\(\alpha\)GDP) can be given as \(17\)

\[
\frac{d[G\alpha GDP]_{\text{post}}}{dt} = v_{GAP1,f,\text{post}} + v_{GAP2,f,\text{post}} + v_{hydrG,f,\text{post}} - v_{regenG,f,\text{post}} \tag{49}
\]

The differential equation for the concentration of IP\(_3\) is \(17\)

\[
\frac{d[IP3]_{\text{post}}}{dt} = v_{DAG1,c,\text{post}} + v_{DAG3,c,\text{post}} - v_{degIP3,\text{post}} \tag{50}
\]

and for the concentration of DAG is \(17\)

\[
\frac{d[DAG]_{\text{post}}}{dt} = v_{DAG2,f,\text{post}} + v_{DAG4,f,\text{post}} - v_{prodAG,f,\text{post}} + v_{prodAG,b,\text{post}} - v_{degDAG,\text{post}} \tag{51}
\]
After IP$_3$ is degraded, PIP$_2$ is regenerated by phosphoinositide 3-kinase (PIKin). The differential equation for the concentration of the degraded IP$_3$ (IP$_3$deg) is \[ \frac{d[IP_{3\text{deg}}]_{\text{post}}}{dt} = v_{\text{deg}IP3,\text{post}} - v_{\text{PIP2},f,\text{post}} + v_{\text{PIP2},b,\text{post}} ; \] (52) for the concentration of PIKin is \[ \frac{d[\text{PIKin}]_{\text{post}}}{dt} = -v_{\text{PIP2},f,\text{post}} + v_{\text{PIP2},b,\text{post}} + v_{\text{PIP2},c,\text{post}} ; \] (53) and for the concentration of the IP$_3$deg-PIKin complex is \[ \frac{d[\text{IP}_3\text{deg-PIKin}]_{\text{post}}}{dt} = v_{\text{PIP2},f,\text{post}} - v_{\text{PIP2},b,\text{post}} - v_{\text{PIP2},c,\text{post}} . \] (54)

After Ca$^{2+}$ binds to DAG lipase (DAGL), the Ca$^{2+}$-DAGL complex binds to DAG and 2-AG synthesis is catalyzed. The equation for the concentration of DAGL is \[ \frac{d[DAGL]_{\text{post}}}{dt} = -v_{\text{DAGL},f,\text{post}} + v_{\text{DAGL},b,\text{post}} ; \] (55) for the concentration of the Ca$^{2+}$-DAGL complex is \[ \frac{d[\text{CaDAGL}]_{\text{post}}}{dt} = v_{\text{DAGL},f,\text{post}} - v_{\text{DAGL},b,\text{post}} - v_{\text{prodAG},f,\text{post}} + v_{\text{prodAG},b,\text{post}} + v_{\text{prodAG},c,\text{post}} ; \] (56) for the concentration of the Ca$^{2+}$-DAG-DAGL complex is \[ \frac{d[\text{CaDAG-DAGL}]_{\text{post}}}{dt} = v_{\text{prodAG},f,\text{post}} - v_{\text{prodAG},b,\text{post}} - v_{\text{prodAG},c,\text{post}} ; \] (57) and, finally, for the concentration of 2-AG is \[ \frac{d[2-\text{AG}]_{\text{post}}}{dt} = v_{\text{prodAG},c,\text{post}} - v_{\text{degAG},\text{post}} . \] (58)

The intermediate variables of the postsynaptic model needed to solve Eq (27)–(58) can be found in Tables L–O and Table Q. The list of postsynaptic reactions can be found in Table P. The parameter values of the postsynaptic model can be found in Tables R–T and initial values in Tables U and V.

**Astrocyte Model**

For the astrocyte model, we utilized previously published [18–19] and extensively tested [39–42] Ca$^{2+}$ signaling models by adding a modified version of a previously published model for IP$_3$ dependence on endocannabinoids [23] and a model for Glu release to the extrasynaptic space [6–10].

We modeled the Ca$^{2+}$ and IP$_3$ concentrations, and the gating variable for IP$_3$R inactivation ($h_{\text{astro}}$) in the astrocyte, and the Glu concentration in the extrasynaptic space. The differential equation for the astrocytic Ca$^{2+}$ concentration is \[ \frac{d[\text{Ca}^{2+}]_{\text{astro}}}{dt} = J_{\text{IP3R,astro}} - J_{\text{SERCA,astro}} + J_{\text{leakER,astro}} ; \] (59) where $J_{\text{IP3R,astro}}$ is the Ca$^{2+}$ flux via IP$_3$Rs from the ER into the cytosol, $J_{\text{SERCA,astro}}$ is the Ca$^{2+}$ flux via SERCA pumps from the cytosol into the ER, and $J_{\text{leakER,astro}}$ is the
Ca\(^{2+}\) leak flux from the ER into the cytosol. The differential equation for the astrocytic IP\(_3\) concentration was modified from previously published equations \(^{23,38}\) and given as

\[
\frac{d[IP_3]_{astro}}{dt} = \frac{IP^{*}_{3,astro} - [IP_3]_{astro}}{τ_{IP_3,astro}} + r_{IP_3,astro}([2-AG]_{post} - AG^{*}_{post}),
\]

where \(IP^{*}_{3,astro}\), \(τ_{IP_3,astro}\), \(r_{IP_3,astro}\), \([2-AG]_{post}\), and \(AG^{*}_{post}\) denote the resting concentration of IP\(_3\), time constant for IP\(_3\) degradation, rate constant of IP\(_3\) production, concentration of the endocannabinoid 2-AG released from the postsynaptic neuron, and resting concentration of 2-AG, respectively. The differential equation for the astrocytic IP\(_3\)R inactivation gating variable is given as \(^{19}\)

\[
\frac{dh_{astro}}{dt} = h_{∞,astro} - h_{astro} \cdot τ_{h,astro},
\]

where \(h_{∞,astro}\) is the steady-state value of the IP\(_3\)R inactivation gating variable and \(τ_{h,astro}\) is the time constant for the IP\(_3\)R inactivation.

We modeled the astrocytic Glu release as exocytosis \(^{43–45}\). The differential equation for the fraction of releasable Glu resources in astrocyte is \(^{7–10}\)

\[
\frac{dR_{rel,astro}}{dt} = k_{recov,astro} \cdot (1 - R_{rel,astro}) - \sum \limits_i P_{rel,astro} \cdot R_{rel,astro} \cdot δ(t - τ_i),
\]

and the Glu concentration in the extrasynaptic space is \(^{9,10}\)

\[
\frac{d[Glu]_{extsyn}}{dt} = -r_{astro} [Glu]_{extsyn} + \sum \limits_i r_{vesext,astro} G_{astro} N_{astro} P_{rel,astro} R_{rel,astro} δ(t - τ_i),
\]

where \(k_{recov,astro}\) is the recovery rate constant from empty to releasable state, \(r_{astro}\) is the Glu clearance rate from the extrasynaptic space, \(r_{vesext,astro}\) is the ratio between the astrocytic vesicular volume and the volume of the extrasynaptic space, \(G_{astro}\) is the Glu concentration per astrocytic vesicle, and \(N_{astro}\) is the number of readily releasable astrocytic vesicles. The astrocytic Glu release occurs at the first time point \(t = τ_i\) such that \([Ca^{2+}]_{astro} ≥ C_{thr,astro}\) and \(\frac{d[Ca^{2+}]_{astro}}{dt} > 0\) at that time point \(τ_i\). The δ function has units of \(1/\text{ms}\).

Intermediate variables needed to solve Eq (59)-(63) can be found in Table W, parameter values in Table X, and initial values in Table Y.
### Table A. Abbreviations.

| Abbreviation | Explanation | Abbreviation | Explanation |
|--------------|-------------|--------------|-------------|
| 2-AG         | 2-arachidonoylglycerol | IP<sub>3</sub>deg | Degraded IP<sub>3</sub> |
| AMPAR        | α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor | IP<sub>3</sub>R | IP<sub>3</sub> receptor |
| ATP          | Adenosine triphosphate | K<sup>+</sup> | Potassium ion |
| Ca<sup>2+</sup> | Calcium ion | K<sub>A</sub> | A-type K<sup>+</sup> channel |
| CaN          | Calcineurin | K<sub>DR</sub> | Delayed rectifier K<sup>+</sup> channel |
| Ca<sub>LHVA</sub> | L-type HVA Ca<sup>2+</sup> channel | L2/3 | Layer 2/3 |
| Ca<sub>LLVA</sub> | L-type LVA Ca<sup>2+</sup> channel | L4 | Layer 4 |
| Ca<sub>NHVA</sub> | N-type HVA Ca<sup>2+</sup> channel | LTD | Long-term depression |
| CB<sub>1</sub>R | Type 1 cannabinoid receptor | LTP | Long-term potentiation |
| DAG          | Diacylglycerol | LVA | Low-voltage-activated |
| DAGL         | DAG lipase | Mg<sup>2+</sup> | Magnesium ion |
| EPSP         | Excitatory postsynaptic potential | mGluR | Metabotropic Glu receptor |
| ER           | Endoplasmic reticulum | mGluR<sub>desens</sub> | Desensitized mGluR |
| G            | G protein | Na<sup>+</sup> | Sodium ion |
| Gα          | G protein with α subunit | Na<sub>p</sub> | Persistent Na<sup>+</sup> channel |
| G<sub>αβγ</sub> | G protein with α, β, and γ subunits | NMDAR | N-methyl-D-aspartate receptor |
| GαGDP        | G protein with α subunit bound with GDP | PIKin | Phosphoinositide 3-kinase |
| GαGTP        | G protein with α subunit bound with GTP | PIP<sub>2</sub> | Phosphatidylinositol 4,5-bisphosphate |
| Gβγ          | G protein with β and γ subunits | PLC | Phospholipase C |
| GAP          | GTPase activating protein | PMCA | Plasma membrane Ca<sup>2+</sup>-ATPase |
| GDP          | Guanosine diphosphate | SERCA | Sarco/ER Ca<sup>2+</sup>-ATPase |
| Glu          | Glutamate | STDP | Spike-timing-dependent plasticity |
| GluN2C/D     | NMDAR containing GluN2C or GluN2D subunits | t-LTD | Spike-timing-dependent LTD |
| GTP          | Guanosine-5’-triphosphate | t-LTP | Spike-timing-dependent LTP |
| HVA          | High-voltage-activated | ΔEPSP | Change in EPSP |
| IP<sub>3</sub> | Inositol 1,4,5-trisphosphate | ΔT | Temporal difference between the pre- and postsynaptic activity |
Table B. Parameter values.

| Name         | Value     | Unit   | Description                                                     | Refs |
|--------------|-----------|--------|-----------------------------------------------------------------|------|
| $A_{\text{stim,post}}$ | 25       | $\text{\mu A/cm}^2$ | External current amplitude to postsynaptic neuron per unit area |      |
| $A_{\text{stim,pre}}$  | 10       | $\text{\mu A/cm}^2$ | External current amplitude to presynaptic neuron per unit area  |      |
| $F$          | 96,485    | $\text{C/mol}$   | Faraday constant                                                |      |
| $N_A$        | $6.0221 \times 10^{23}$ | $1/\text{mol}$ | Avogadro’s constant                                             | 14   |
| $R$          | 8.3145    | $\text{J/Kmol}$  | Molar gas constant                                              |      |
| $T_{\text{celsius}}$ | 36       | $^\circ\text{C}$  | Temperature                                                     | 14   |
| $z$          | 2         | 1      | Valence of $\text{Ca}^{2+}$ ion                                 |      |
Table C. Intermediate variables of presynaptic channel model.

| Intermediate variable | Description | Refs |
|-----------------------|-------------|------|
| $\sigma_{s,Na,\text{pre}} = \frac{1}{1 + \exp \left( \frac{V_{\text{pre}} + V_{\text{rev. Na, pre}} + V_{\text{shift, pre}}}{V_{\text{ed, Na, pre}}} \right)}$ | Shift in presynaptic Na$^+$ inactivation time constant | 2 |
| $h_{\infty,Na,\text{pre}} = \frac{1}{1 + \exp \left( \frac{V_{\text{pre}} + 45 + V_{\text{shift, pre}}}{3} \right)}$ | Steady-state value of presynaptic Na$^+$ inactivation gating variable | 2 |
| $m_{\infty,Na,\text{pre}} = \frac{1}{1 + \exp \left( -\frac{V_{\text{pre}} + 40 + V_{\text{shift, pre}}}{3} \right)}$ | Steady-state value of presynaptic Na$^+$ activation gating variable | 2 |
| $s_{\infty,Na,\text{pre}} = \frac{1}{1 + \exp \left( \frac{V_{\text{pre}} + 44 + V_{\text{shift, pre}}}{3} \right)}$ | Steady-state value of presynaptic Na$^+$ inactivation gating variable | 2 |
| $n_{\infty,K,\text{pre}} = \frac{1}{1 + \exp \left( -\frac{V_{\text{pre}} + 40 + V_{\text{shift, pre}}}{3} \right)}$ | Steady-state value of presynaptic K$^+$ activation gating variable | 2 |
| $n_{\infty,K,2,\text{pre}} = \frac{1}{1 + \exp \left( -\frac{V_{\text{pre}} + 40 + V_{\text{shift, pre}}}{3} \right)}$ | Steady-state value of presynaptic K$^+$ activation gating variable | 2 |
| $\alpha_{h,\text{CaNHVA, pre}} = 0.00016 \exp \left( -\frac{V_{\text{pre}}}{48.4} \right)$ | Transition rate of presynaptic Ca$^{2+}$ channel’s inactivation gate from non-permissive to permissive state | 1 |
| $\alpha_{m,\text{CaNHVA, pre}} = 0.1967 \frac{-V_{\text{pre}} + 19.88}{\exp \left( -\frac{V_{\text{pre}} + 19.88}{10} \right) - 1}$ | Transition rate of presynaptic Ca$^{2+}$ channel’s activation gate from non-permissive to permissive state | 1 |
| $\alpha_{mt,\text{CaNHVA, pre}} = \exp \left( 0.0378 z_{m,\text{pre}} (V_{\text{pre}} - V_{1/2m,\text{pre}}) \right)$ | Rate used in calculation of presynaptic Ca$^{2+}$ activation time constant | 1 |
| $\beta_{h,\text{CaNHVA, pre}} = \frac{1}{1 + \exp \left( -\frac{V_{\text{pre}} + 39}{10} \right)}$ | Transition rate of presynaptic Ca$^{2+}$ channel’s inactivation gate from permissive to non-permissive state | 1 |
| $\beta_{m,\text{CaNHVA, pre}} = 0.046 \exp \left( -\frac{V_{\text{pre}}}{20.73} \right)$ | Transition rate of presynaptic Ca$^{2+}$ channel’s activation gate from permissive to non-permissive state | 1 |
| $\beta_{mt,\text{CaNHVA, pre}} = \exp \left( 0.0378 z_{m,\text{pre}} g_{mm,\text{pre}} (V_{\text{pre}} - V_{1/2m,\text{pre}}) \right)$ | Rate used in calculation of presynaptic Ca$^{2+}$ activation time constant | 1 |
| $h_{\infty,\text{CaNHVA, pre}} = \frac{\alpha_{h,\text{CaNHVA, pre}}}{\alpha_{h,\text{CaNHVA, pre}} + \beta_{h,\text{CaNHVA, pre}}}$ | Steady-state value of presynaptic Ca$^{2+}$ inactivation gating variable | 1 |
| $m_{\infty,\text{CaNHVA, pre}} = \frac{\alpha_{m,\text{CaNHVA, pre}}}{\alpha_{m,\text{CaNHVA, pre}} + \beta_{m,\text{CaNHVA, pre}}}$ | Steady-state value of presynaptic Ca$^{2+}$ activation gating variable | 1 |
| $h_{\infty,\text{CaNHVA, 2, pre}} = \frac{K_{\text{inh, pre}}}{K_{\text{inh, pre}} + [Ca^{2+}]_{\text{CaNHVA, pre}}}$ | Steady-state value of presynaptic Ca$^{2+}$ inactivation gating variable | 1 |
| $\tau_{m,\text{CaNHVA, pre}} = \max \left( \frac{\tau_{m,\text{min, pre}}}{5 \gamma_{\text{CaNHVA, pre}}}, \frac{\tau_{m,\text{max, pre}}}{5 \gamma_{\text{CaNHVA, pre}}}, \frac{\beta_{mt,\text{CaNHVA, pre}}}{\alpha_{m,\text{CaNHVA, pre}} (1 + \alpha_{mt,\text{CaNHVA, pre}})} \right)$ | Time constant for presynaptic Ca$^{2+}$ activation | 1 |
### Table D. Presynaptic channel and receptor currents.

| Intermediate variable | Description | Refs |
|-----------------------|-------------|------|
| $\nu_{\text{pre}} = \frac{V_{\text{pre}}}{c_{V,\text{pre}}}$ | Scaling of presynaptic membrane potential used in Goldman-Hodgkin-Katz current equation (unitless) | 1 |
| $e_{\text{pre}} = \begin{cases} \frac{\nu_{\text{pre}}^2}{2} - 1, & \text{if } |\nu_{\text{pre}}| < 0.0001 \\ \frac{\nu_{\text{pre}}}{1 - \exp(\nu_{\text{pre}})}, & \text{otherwise} \end{cases}$ | Equation dealing with Goldman-Hodgkin-Katz current equation near 0 mV and otherwise | 1 |
| $f_{\text{ghk,pre}} = c_{V,\text{pre}} \left( 1 - \frac{[Ca^{2+}]_{\text{CaNHVA,pre}}}{C_{\text{Ca,ext,pre}}} \exp (\nu_{\text{pre}}) \right) e_{\text{pre}}$ | Driving force of Goldman-Hodgkin-Katz current equation used in calculation of presynaptic CaNHVA current | 1 |
| $I_{\text{CaNHVA,pre}} = g_{\text{CaNHVA,pre}} m_{\text{CaNHVA,pre}}^2 h_{\text{CaNHVA,pre}} h_{\infty_{\text{CaNHVA,pre}}} \frac{V_{\text{pre}} - V_{\text{CaNHVA,pre}}}{f_{\text{ghk,pre}}}$ | Presynaptic CaNHVA current density | 1 |
| $I_{\text{K,pre}} = g_{K,\text{pre}} h_{K,\text{pre}}^3 (V_{\text{pre}} - V_{K,\text{pre}}) + g_{K,2,\text{pre}} h_{K,2,\text{pre}}^3 (V_{\text{pre}} - V_{K,\text{pre}})$ | Presynaptic K+ current density | 2 |
| $I_{\text{L,pre}} = g_{L,\text{pre}} (V_{\text{pre}} - V_{L,\text{pre}})$ | Presynaptic leak current density | 2 |
| $I_{\text{Na,pre}} = g_{Na,\text{pre}} m_{\text{Na,pre}}^3 h_{Na,\text{pre}} h_{\infty_{\text{Na,pre}}} (V_{\text{pre}} - V_{Na,\text{pre}})$ | Presynaptic Na+ current density | 2 |
| $I_{\text{Ca,NMDAR,pre}} = \begin{cases} 0, & \text{if } V_{\text{pre}} \geq V_{\text{NMDAR,pre}} \\ 0.1 g_{\text{NMDAR,pre}} R_{A2,\text{O,pre}} \times \frac{V_{\text{pre}} - V_{\text{NMDAR,pre}}}{(V_{\text{pre}} - V_{NMDAR,pre})}, & \text{otherwise} \end{cases}$ | Ca2+ current density via presynaptic NMDARs | 46 47 |
| $I_{\text{Na,NMDAR,pre}} = \begin{cases} 0, & \text{if } V_{\text{pre}} \geq V_{\text{NMDAR,pre}} \\ 0.9 g_{\text{NMDAR,pre}} R_{A2,\text{O,pre}} \times \frac{V_{\text{pre}} - V_{\text{NMDAR,pre}}}{(V_{\text{pre}} - V_{NMDAR,pre})}, & \text{otherwise} \end{cases}$ | Na+ current density via presynaptic NMDARs | 46 47 |
| Reaction | Description | Refs |
|----------|-------------|------|
| \text{Glu}_{\text{NMDAR},\text{pre}} + \text{R}_{\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{pre}} | Presynaptic NMDAR agonist (Glu) binding | 3,4 |
| \text{Glu}_{\text{NMDAR},\text{pre}} + \text{R}_{\text{A},\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{pre}} | Presynaptic NMDAR agonist (Glu) binding | 3,4 |
| \text{R}_{\text{A},\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{d1},\text{pre}} | Desensitized state of presynaptic NMDAR | 3,4 |
| \text{R}_{\text{A},\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{d2},\text{pre}} | Desensitized state of presynaptic NMDAR | 3,4 |
| \text{R}_{\text{A},\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{f},\text{pre}} | Gating-associated conformational changes of presynaptic GluN1 subunit of NMDAR | 3,4 |
| \text{R}_{\text{A},\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{s},\text{pre}} | Gating-associated conformational changes of presynaptic GluN2 subunit of NMDAR | 3,4 |
| \text{R}_{\text{A},\text{f},\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{O},\text{pre}} | Gating-associated conformational changes of presynaptic GluN2 subunit of NMDAR | 3,4 |
| \text{Glu}_{\text{NMDAR},\text{pre}} + \text{R}_{\text{Mg},\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{Mg},\text{pre}} | Presynaptic Mg$^{2+}$-blocked NMDAR agonist (Glu) binding | 3,4 |
| \text{Glu}_{\text{NMDAR},\text{pre}} + \text{R}_{\text{A},\text{Mg},\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{Mg},\text{pre}} | Presynaptic Mg$^{2+}$-blocked NMDAR agonist (Glu) binding | 3,4 |
| \text{R}_{\text{A},\text{Mg},\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{d1},\text{Mg},\text{pre}} | Desensitized state of presynaptic Mg$^{2+}$-blocked NMDAR | 3,4 |
| \text{R}_{\text{A},\text{Mg},\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{d2},\text{Mg},\text{pre}} | Desensitized state of presynaptic Mg$^{2+}$-blocked NMDAR | 3,4 |
| \text{R}_{\text{A},\text{Mg},\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{f},\text{Mg},\text{pre}} | Gating-associated conformational changes of presynaptic GluN1 subunit of Mg$^{2+}$-blocked NMDAR | 3,4 |
| \text{R}_{\text{A},\text{Mg},\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{s},\text{Mg},\text{pre}} | Gating-associated conformational changes of presynaptic GluN2 subunit of Mg$^{2+}$-blocked NMDAR | 3,4 |
| \text{R}_{\text{A},\text{O},\text{Mg},\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{s},\text{Mg},\text{pre}} | Gating-associated conformational changes of presynaptic GluN1 subunit of Mg$^{2+}$-blocked NMDAR | 3,4 |
| \text{R}_{\text{A},\text{O},\text{Mg},\text{pre}} \rightleftharpoons \text{R}_{\text{A},\text{o},\text{Mg},\text{pre}} | Gating-associated conformational changes of presynaptic GluN1 subunit of Mg$^{2+}$-blocked NMDAR | 3,4 |
Table F. Intermediate variables of presynaptic Glu release model and NMDAR model.

| Intermediate variable | Description |
|-----------------------|-------------|
| $f_{\text{pre}} = \frac{[X]_{\text{ac,pre}}}{N_{\text{total,pre}}}$ | Fraction of presynaptic Glu release inhibition |
| $[\text{Glu}]_{\text{NMDAR,pre}} = f_{\text{Glu,pre}}[\text{Glu}]_{\text{synclien}} + [\text{Glu}]_{\text{extsyn}}$ | Total concentration of Glu that presynaptic NMDARs receives |
| $k_{\text{Mg,f,pre}} = 0.00061 \exp \left(-\frac{V_{\text{pre}}}{17}\right)$ | Rate of presynaptic NMDAR blocking by external Mg$^{2+}$ |
| $k_{\text{Mg,b,pre}} = 5.4 \exp \left(\frac{V_{\text{pre}}}{47}\right)$ | Rate of presynaptic NMDAR unblocking by external Mg$^{2+}$ |
| $k_{s,f,pre} = k_{s,f,0,pre} \exp \left(\frac{V_{\text{pre}} + 100}{175}\right)$ | Rate of gating-associated conformational changes of presynaptic GluN2 subunit of NMDAR |
| $\nu_{2\text{k,pre}} = 2k_{\text{on,pre}}[\text{Glu}]_{\text{NMDAR,pre}}R_{\text{pre}}$ | Reaction rates of Glu binding and unbinding to presynaptic NMDAR |
| $\nu_{2\text{off,pre}} = k_{\text{off,pre}}R_{\text{A}_2,pre}$ | Reaction rates of Glu binding and unbinding to presynaptic NMDAR |
| $\nu_{\text{on,pre}} = k_{\text{on,pre}}[\text{Glu}]_{\text{NMDAR,pre}}R_{\text{A}_2,pre}$ | Reaction rates of Glu binding and unbinding to presynaptic NMDAR |
| $\nu_{2\text{off,pre}} = 2k_{\text{on,pre}}R_{\text{A}_2,pre}$ | Reaction rates of Glu binding and unbinding to presynaptic NMDAR |
| $v_{d1,f,pre} = k_{d1,f,pre}R_{\text{A}_2,pre}$ | Reaction rates into and out of desensitized state of presynaptic NMDAR |
| $v_{d1,b,pre} = k_{d1,b,pre}R_{\text{A}_2,d1,pre}$ | Reaction rates into and out of desensitized state of presynaptic NMDAR |
| $v_{d2,f,pre} = k_{d2,f,pre}R_{\text{A}_2,pre}$ | Reaction rates into and out of desensitized state of presynaptic NMDAR |
| $v_{d2,b,pre} = k_{d2,b,pre}R_{\text{A}_2,d2,pre}$ | Reaction rates into and out of desensitized state of presynaptic NMDAR |
| $v_{1,f,pre} = k_{1,f,pre}R_{\text{A}_2,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN1 subunit of NMDAR |
| $v_{1,b,pre} = k_{1,b,pre}R_{\text{A}_2,f,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN1 subunit of NMDAR |
| $v_{s,f,pre} = k_{s,f,pre}R_{\text{A}_2,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN2 subunit of NMDAR |
| $v_{s,b,pre} = k_{s,b,pre}R_{\text{A}_2,s,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN2 subunit of NMDAR |
| $v_{2,f,pre} = k_{2,f,pre}R_{\text{A}_2,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN1 subunit of NMDAR |
| $v_{2,b,pre} = k_{2,b,pre}R_{\text{A}_2,s,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN1 subunit of NMDAR |
| $v_{2\text{k,Mg,pre}} = 2k_{\text{on,Mg,pre}}[\text{Glu}]_{\text{NMDAR,pre}}R_{\text{Mg,pre}}$ | Reaction rates of Glu binding and unbinding to presynaptic Mg$^{2+}$-blocked NMDAR |
| $v_{2\text{off,Mg,pre}} = k_{\text{off,Mg,pre}}R_{\text{A}_2,Mg,pre}$ | Reaction rates of Glu binding and unbinding to presynaptic Mg$^{2+}$-blocked NMDAR |
| $v_{\text{k,Mg,pre}} = k_{\text{on,Mg,pre}}[\text{Glu}]_{\text{NMDAR,pre}}R_{\text{Mg,pre}}$ | Reaction rates of Glu binding and unbinding to presynaptic Mg$^{2+}$-blocked NMDAR |
| $v_{\text{off,Mg,pre}} = k_{\text{off,Mg,pre}}R_{\text{A}_2,Mg,pre}$ | Reaction rates of Glu binding and unbinding to presynaptic Mg$^{2+}$-blocked NMDAR |
| $v_{\text{d1,Mg,pre}} = k_{d1,f,pre}R_{\text{A}_2,Mg,pre}$ | Reaction rates into and out of desensitized state of presynaptic Mg$^{2+}$-blocked NMDAR |
| $v_{\text{d1,Mg,pre}} = k_{d1,b,pre}R_{\text{A}_2,d1,Mg,pre}$ | Reaction rates into and out of desensitized state of presynaptic Mg$^{2+}$-blocked NMDAR |
| $v_{\text{d2,Mg,pre}} = k_{d2,f,pre}R_{\text{A}_2,Mg,pre}$ | Reaction rates into and out of desensitized state of presynaptic Mg$^{2+}$-blocked NMDAR |
| $v_{\text{d2,Mg,pre}} = k_{d2,b,pre}R_{\text{A}_2,d2,Mg,pre}$ | Reaction rates into and out of desensitized state of presynaptic Mg$^{2+}$-blocked NMDAR |
| $v_{1\text{Mg,pre}} = k_{1,f,pre}R_{\text{A}_2,Mg,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN1 subunit of Mg$^{2+}$-blocked NMDAR |
| $v_{1\text{Mg,pre}} = k_{1,b,pre}R_{\text{A}_2,f,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN1 subunit of Mg$^{2+}$-blocked NMDAR |
| $v_{s\text{Mg,pre}} = k_{s,f,pre}R_{\text{A}_2,Mg,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN2 subunit of Mg$^{2+}$-blocked NMDAR |
| $v_{s\text{Mg,pre}} = k_{s,b,pre}R_{\text{A}_2,s,Mg,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN2 subunit of Mg$^{2+}$-blocked NMDAR |
| $v_{2\text{Mg,pre}} = k_{2,f,pre}R_{\text{A}_2,Mg,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN1 subunit of Mg$^{2+}$-blocked NMDAR |
| $v_{2\text{Mg,pre}} = k_{2,b,pre}R_{\text{A}_2,s,Mg,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN1 subunit of Mg$^{2+}$-blocked NMDAR |
| $v_{\text{Mg,pre}} = k_{\text{Mg,pre}}R_{\text{A}_2,O,Mg,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN1 subunit of Mg$^{2+}$-blocked NMDAR |
| $v_{\text{Mg,pre}} = k_{\text{Mg,pre}}R_{\text{A}_2,O,Mg,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN1 subunit of Mg$^{2+}$-blocked NMDAR |
| $v_{\text{Mg,pre}} = k_{\text{Mg,pre}}R_{\text{A}_2,O,Mg,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN1 subunit of Mg$^{2+}$-blocked NMDAR |
| $v_{\text{Mg,pre}} = k_{\text{Mg,pre}}R_{\text{A}_2,O,Mg,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN1 subunit of Mg$^{2+}$-blocked NMDAR |
| $v_{\text{Mg,pre}} = k_{\text{Mg,pre}}R_{\text{A}_2,O,Mg,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN1 subunit of Mg$^{2+}$-blocked NMDAR |
| $v_{\text{Mg,pre}} = k_{\text{Mg,pre}}R_{\text{A}_2,O,Mg,pre}$ | Reaction rates of gating-associated conformational changes of presynaptic GluN1 subunit of Mg$^{2+}$-blocked NMDAR |

Refs:

4 | 48 | 3,4 | 3,4 | 3,4 | 3,4 | 3,4 | 3,4 | 3,4
| Parameter        | Value | Unit       | Description                                                    | Refs          |
|------------------|-------|------------|----------------------------------------------------------------|---------------|
| $C_{m,\text{pre}}$ | 1.5   | $\mu$F/cm² | Presynaptic membrane capacitance per unit area                  | [2]           |
| $g_{\text{CaNHVA,pre}}$ | 0.3   | mS/cm²     | Maximum conductance of presynaptic Ca_{NHVA} current per unit area | [1]           |
| $g_{K,\text{pre}}$   | 20    | mS/cm²     | Maximum conductance of presynaptic K⁺ current per unit area     | [2]: 120 mS/cm² |
| $g_{K_{\text{2,pre}}}$ | 20    | mS/cm²     | Maximum conductance of presynaptic K⁺ current per unit area     | [2]: 120 mS/cm² |
| $g_{L,\text{pre}}$   | 0.2   | mS/cm²     | Leak conductance of presynaptic neuron per unit area            | [2]: 0.1 mS/cm² |
| $g_{Na,\text{pre}}$  | 30    | mS/cm²     | Maximum conductance of presynaptic Na⁺ current per unit area    | [2]: 200 mS/cm² |
| $g_{\text{NMDAR,pre}}$ | 0.1   | mS/cm²     | Maximum conductance of presynaptic NMDAR per unit area          | [49]: 0.014 mS/cm² |
| $\tau_{h,\text{CaNHVA,pre}}$ | 80    | ms         | Time constant for presynaptic Ca_{NHVA} inactivation            | [1]           |
| $\tau_{m,\text{Na,pre}}$ | 0.05  | ms         | Time constant for presynaptic Na⁺ inactivation                  | [2]           |
| $\tau_{n,\text{K,pre}}$  | 1     | ms         | Time constant for presynaptic K⁺ activation                     | [2]           |
| $\tau_{n,\text{K_{\text{2,pre}}}}$ | 10    | ms         | Time constant for presynaptic K⁺ activation                     | [2]           |
| $\tau_{s,\text{Na,pre}}$  | 30    | ms         | Time constant for presynaptic Na⁺ inactivation                  | [2]           |
| $\tau_{sb,\text{Na,pre}}$  | 0.1   | ms         | Time constant for presynaptic Na⁺ inactivation                  | [2]: 0.5 ms   |
| $V_{K,\text{pre}}$   | -77   | mV         | Reversal potential of presynaptic K⁺ current                    | [2]           |
| $V_{L,\text{pre}}$   | -60   | mV         | Leak reversal potential of presynaptic neuron                   | [2]: -70 mV   |
| $V_{Na,\text{pre}}$  | 50    | mV         | Reversal potential of presynaptic Na⁺ current                   | [2]: 40 mV, 70 mV |
| $V_{\text{NMDAR,pre}}$ | 0     | mV         | Reversal potential of presynaptic NMDAR current                 | [16]          |
| $V_{sd,\text{Na,pre}}$  | 1     | mV         | Shift in presynaptic membrane potential used in calculation of Na⁺ current | [2]           |
| $V_{\text{shift,pre}}$   | -10   | mV         | Shift in presynaptic membrane potential                         | [2]: 0 mV     |
| $V_{sv,\text{Na,pre}}$  | 10    | mV         | Shift in presynaptic membrane potential used in calculation of Na⁺ current | [2]: 30 mV    |
Table H. Parameter values of presynaptic Ca\textsuperscript{2+} model.

| Parameter          | Value | Unit       | Description                                                                 | Refs |
|--------------------|-------|------------|-----------------------------------------------------------------------------|------|
| \(a_{0\text{m,pre}}\) | 0.03  | \(\frac{1}{\text{ms}}\) | Parameter used in calculation of presynaptic Ca\textsubscript{NHVA} activation time constant | 1    |
| \(c_{\text{Ca,pre}}\) | \(\frac{zF \lambda_{\text{pre}}}{k_{\text{Ca,pre}}}\) | \(\mu\text{A ms}^{\text{cm}^{2}}\mu\text{M}\) | Presynaptic scaling factor to convert from units \(\frac{\mu\text{A}}{\text{cm}^{2}}\) to \(\mu\text{M ms}\) | 1    |
| \(c_{V,\text{pre}}\) | \(k_{\text{V,pre}}R(T_{\text{celsius}} + 273.15)\) | mV | Presynaptic scaling factor to convert from units mV to 1 used in calculation of Goldman-Hodgkin-Katz current equation | 1    |
| \(C_{\text{ext,pre}}\) | 2.000 | \(\mu\text{M}\) | Ca\textsuperscript{2+} concentration outside presynaptic neuron | 1    |
| \(C_{\text{rest,pre}}\) | 0.05  | \(\mu\text{M}\) | Presynaptic resting Ca\textsuperscript{2+} concentration | 1    |
| \(d_{\text{pre}}\) | 0.1   | \(\mu\text{m}\) | Depth of presynaptic axonal shell | 1    |
| \(g_{\text{nm,pre}}\) | 0.1   | 1 | Parameter used in calculation of presynaptic Ca\textsubscript{NHVA} activation time constant | 1    |
| \(k_{\text{Ca,pre}}\) | 10,000 | 1 | Presynaptic scaling factor used in calculation of \(c_{\text{Ca,pre}}\) | 1    |
| \(k_{V,\text{pre}}\) | 1,000 | 1 | Presynaptic scaling factor used in calculation of \(c_{V,\text{pre}}\) | 1    |
| \(K_{\text{inh,pre}}\) | 1     | \(\mu\text{M}\) | Presynaptic Ca\textsubscript{NHVA} channel dissociation constant (inhibition) | 1    |
| \(\tau_{\text{Ca,pre}}\) | 100   | ms | Time constant of presynaptic pump | 1    |
| \(\tau_{\text{m,\text{min,pre}}}\) | 0.2   | ms | Minimum value for presynaptic Ca\textsubscript{NHVA} activation time constant | 1    |
| \(V_{1/2\text{m,pre}}\) | −14   | mV | Half-activation potential of presynaptic Ca\textsubscript{NHVA} channel | 1    |
| \(z_{\text{m,pre}}\) | 2     | 1 | Parameter used in calculation of presynaptic Ca\textsubscript{NHVA} activation time constant | 1    |
| Parameter       | Value  | Unit   | Description                                                                 | Refs  |
|-----------------|--------|--------|------------------------------------------------------------------------------|-------|
| $k_{d1,f,pre}$  | 0.055  | $\frac{1}{\text{ms}}$ | Rate constant into desensitized state of presynaptic NMDAR                  | 3: 0.55 $\frac{1}{\text{ms}}$ |
| $k_{d1,b,pre}$  | 0.0814 | $\frac{1}{\text{ms}}$ | Rate constant out of desensitized state of presynaptic NMDAR                | 3     |
| $k_{d2,f,pre}$  | 0.0112 | $\frac{1}{\text{ms}}$ | Rate constant into desensitized state of presynaptic NMDAR                  | 3: 0.112 $\frac{1}{\text{ms}}$ |
| $k_{d2,b,pre}$  | 0.00091| $\frac{1}{\text{ms}}$ | Rate constant out of desensitized state of presynaptic NMDAR                | 3     |
| $k_{f,f,pre}$   | 2.836  | $\frac{1}{\text{ms}}$ | Rate constant for gating-associated conformational changes of presynaptic GluN1 subunit of NMDAR | 3,4   |
| $k_{f,b,pre}$   | 0.175  | $\frac{1}{\text{ms}}$ | Rate constant for gating-associated conformational changes of presynaptic GluN1 subunit of NMDAR | 3,4   |
| $k_{on,pre}$    | 0.00283| $\frac{1}{\mu\text{M ms}}$ | Rate constant for agonist (Glu) binding to presynaptic NMDAR                | 3,4   |
| $k_{off,pre}$   | 0.0381 | $\frac{1}{\text{ms}}$ | Rate constant for agonist (Glu) unbinding from presynaptic NMDAR             | 3,4   |
| $k_{s,f,0,pre}$ | 0.048  | $\frac{1}{\text{ms}}$ | Rate constant for gating-associated conformational changes of presynaptic GluN2 subunit of NMDAR | 3,4   |
| $k_{s,b,pre}$   | 0.23   | $\frac{1}{\text{ms}}$ | Rate constant for gating-associated conformational changes of presynaptic GluN2 subunit of NMDAR | 3,4   |
### Table J. Parameter values of presynaptic Glu release model.

| Parameter          | Value | Unit   | Description                                                                 | Refs |
|--------------------|-------|--------|-----------------------------------------------------------------------------|------|
| $C_{\text{thr,pre}}$ | 3     | µM     | Ca$^{2+}$ threshold concentration of Glu release in presynaptic neuron      |      |
| $C_{\text{max,pre}}$ | 2     | µM     | Total concentration of presynaptic CaN                                      | 50   |
| $f_{\text{Glu,pre}}$ | 0.1   |        | Factor representing spillover of Glu from synaptic cleft that presynaptic NMDAR receives |      |
| $G_{\text{pre}}$ | 1.092 | 1      | Number of Glu per presynaptic vesicle                                       | 51   |
| $k_1_{\text{pre}}$ | 0.001 | $\frac{1}{\text{µM} \cdot \text{ms}}$ | Rate constant for Ca$^{2+}$ activation of presynaptic CaN                   | 50   |
| $k_2_{\text{pre}}$ | 0.002 | $\frac{1}{\text{ms}}$ | Rate constant for inactivation of presynaptic CaN                           | 50, 0.012 $\frac{1}{\text{ms}}$ |
| $k_f_{\text{pre}}$ | 0.0075 | $\frac{1}{\text{ms}}$ | Presynaptic facilitation rate constant                                        |      |
| $k_{\text{Glu,pre}}$ | $10^{-6}$ | 1    | Presynaptic scaling factor to convert from units M to µM                    |      |
| $k_{\text{recov,pre}}$ | 0.0075 | $\frac{1}{\text{ms}}$ | Presynaptic recovery rate constant from empty to releasable state            | 8    |
| $K_{\text{A,pre}}$ | 2     | µM     | Presynaptic CaN concentration producing half occupation                      |      |
| $K_{\text{rel,pre}}$ | 5     | µM     | Presynaptic Ca$^{2+}$ concentration producing half occupation used in calculation of Glu release | 8: 20 µM |
| $n_1_{\text{pre}}$ | 2     | 1      | Presynaptic Hill coefficient                                                 | 8: 4 |
| $n_2_{\text{pre}}$ | 2     | 1      | Presynaptic Hill coefficient                                                 |      |
| $N_{\text{pre}}$ | 2     | 1      | Number of readily releasable presynaptic vesicles                           | 52: 4.6 ± 3.0 |
| $p_1_{\text{pre}}$ | $3 \times 10^{-5}$ | $\frac{1}{\text{ms}}$ | Rate constant for presynaptic protein activation affecting vesicular release |      |
| $V_{\text{syncleft}}$ | $2 \times 10^{-18}$ | 1    | Volume of synaptic cleft                                                    | 55: 0.7 $\times 10^{-18}$, 1 $- 8 \times 10^{-18}$, 1, 52: 0.76 $\times 10^{-18}$ |
| $X_{\text{total,pre}}$ | 0.1   | µM     | Total concentration of presynaptic protein affecting vesicular release       |      |
| Variable                  | Initial value | Unit | Description                                                                 | Refs |
|--------------------------|---------------|------|------------------------------------------------------------------------------|------|
| $[\text{Ca}^{2+}]_{\text{CaNHVA,pre}}$ | 0.082523      | µM   | Presynaptic Ca$_{\text{NHVA}}$-mediated Ca$^{2+}$ concentration             |      |
| $[\text{Ca}^{2+}]_{\text{NMDAR,pre}}$   | 0.05          | µM   | Presynaptic NMDAR-mediated Ca$^{2+}$ concentration                           |      |
| $[\text{CaN}]_{\text{pre}}$            | $1.2499 \times 10^{-4}$ | µM   | Presynaptic CaN concentration                                               |      |
| $[\text{Glu}]_{\text{syncleft}}$       | 0             | µM   | Concentration of Glu in synaptic cleft                                       |      |
| $h_{\text{CaNHVA,pre}}$                | $h_{\infty, \text{CaNHVA,pre}}$ | 1    | Gating variable for presynaptic Ca$_{\text{NHVA}}$ inactivation             | 1    |
| $h_{\text{Na,pre}}$                    | $h_{\infty, \text{Na,pre}}$ | 1    | Gating variable for presynaptic Na$^+$ inactivation                          | 2    |
| $m_{\text{CaNHVA,pre}}$                | $m_{\infty, \text{CaNHVA,pre}}$ | 1    | Gating variable for presynaptic Ca$_{\text{NHVA}}$ activation             | 1    |
| $m_{\text{Na,pre}}$                    | $m_{\infty, \text{Na,pre}}$ | 1    | Gating variable for presynaptic Na$^+$ activation                          | 2    |
| $n_{\text{K,pre}}$                     | $n_{\infty, \text{K,pre}}$ | 1    | Gating variable for presynaptic K$^+$ activation                         | 2    |
| $n_{\text{K,2,pre}}$                   | $n_{\infty, \text{K,2,pre}}$ | 1    | Gating variable for presynaptic K$^+$ activation                         | 2    |
| $P_{\text{rel,pre}}$                   | 0             | 1    | Release probability of presynaptic Glu vesicles                             |      |
| $R_{\text{pre}}$                       | 0             | 1    | Fraction of presynaptic NMDARs in closed state                             |      |
| $R_{\text{A,pre}}$                     | 0             | 1    | Fraction of presynaptic NMDARs in single liganded state                   |      |
| $R_{\text{A,2,pre}}$                   | 0             | 1    | Fraction of presynaptic NMDARs in fully liganded state                    |      |
| $R_{\text{A,2,d1,pre}}$                | 0             | 1    | Fraction of presynaptic NMDARs in desensitized state                      |      |
| $R_{\text{A,2,d2,pre}}$                | 0             | 1    | Fraction of presynaptic NMDARs in desensitized state                      |      |
| $R_{\text{A,2,f,pre}}$                 | 0             | 1    | Fraction of presynaptic NMDARs in faster conformational change of GluN1 subunit |      |
| $R_{\text{A,2,s,pre}}$                 | 0             | 1    | Fraction of presynaptic NMDARs in slower conformational change of GluN2 subunit |      |
| $R_{\text{A,2,O,pre}}$                 | 0             | 1    | Fraction of presynaptic NMDARs in open state                             |      |
| $R_{\text{A,Mg,pre}}$                  | 0             | 1    | Fraction of presynaptic NMDARs in single liganded Mg$^{2+}$-blocked state |      |
| $R_{\text{A,2,Mg,pre}}$                | 0             | 1    | Fraction of presynaptic NMDARs in fully liganded Mg$^{2+}$-blocked state  |      |
| $R_{\text{A,2,d1,Mg,pre}}$              | 0             | 1    | Fraction of presynaptic NMDARs in desensitized Mg$^{2+}$-blocked state  |      |
| $R_{\text{A,2,d2,Mg,pre}}$              | 0             | 1    | Fraction of presynaptic NMDARs in desensitized Mg$^{2+}$-blocked state  |      |
| $R_{\text{A,2,f,Mg,pre}}$               | 0             | 1    | Fraction of presynaptic NMDARs in faster conformational change of Mg$^{2+}$-blocked GluN1 subunit |      |
| $R_{\text{A,2,s,Mg,pre}}$               | 0             | 1    | Fraction of presynaptic NMDARs in slower conformational change of Mg$^{2+}$-blocked GluN2 subunit |      |
| $R_{\text{A,2,O,Mg,pre}}$               | 0             | 1    | Fraction of presynaptic NMDARs in Mg$^{2+}$-blocked state                |      |
| $R_{\text{Mg,pre}}$                    | 1             | 1    | Fraction of presynaptic NMDARs in closed Mg$^{2+}$-blocked state         |      |
| $R_{\text{rel,pre}}$                   | 1             | 1    | Fraction of releasable presynaptic vesicles                              | 2    |
| $s_{\text{Na,pre}}$                    | $s_{\infty, \text{Na,pre}}$ | 1    | Gating variable for presynaptic Na$^+$ inactivation                          | 2    |
| $V_{\text{pre}}$                       | $-59.9969$    | mV   | Presynaptic membrane potential                                             |      |
| $[X]_{\text{ac,pre}}$                  | 0             | µM   | Concentration of presynaptic active protein affecting vesicular release  |      |
Table L. Intermediate variables of postsynaptic channel model.

| Intermediate variable | Description | Ref |
|-----------------------|-------------|-----|
| $h_{\infty,Na,soma,post} = \frac{1}{1 + \exp \left( \frac{V_{soma,post} + 23}{11.5} \right)}$ | Steady-state value of postsynaptic Na\(^+\) inactivation gating variable in the soma | 14 |
| $m_{\infty,Na,soma,post} = \frac{1}{1 + \exp \left( - \frac{V_{soma,post} + 17}{11} \right)}$ | Steady-state value of postsynaptic Na\(^+\) activation gating variable in the soma | 14 |
| $m_{\infty,KDR,soma,post} = \frac{1}{1 + \exp \left( - \frac{V_{soma,post} + 17}{13.6} \right)}$ | Steady-state value of postsynaptic K\(_{DR}\) activation gating variable in the soma | 14 |
| $n_{\infty,NaP,soma,post} = \frac{1}{1 + \exp \left( - \frac{V_{soma,post} + 50}{8} \right)}$ | Steady-state value of postsynaptic Na\(_P\) activation gating variable in the soma | 14 |
| $h_{\infty,KA,dend,post} = \frac{1}{1 + \exp \left( V_{dend,post} + 49 \right)}$ | Steady-state value of postsynaptic K\(_A\) activation gating variable in the dendrite | 14 |
| $m_{\infty,KA,dend,post} = \frac{1}{1 + \exp \left( - \frac{V_{dend,post} + 40}{8.5} \right)}$ | Steady-state value of postsynaptic K\(_A\) activation gating variable in the dendrite | 14 |
| $h_{\infty,Na,dend,post} = \frac{1}{1 + \exp \left( V_{dend,post} + 23 \right)}$ | Steady-state value of postsynaptic Na\(^+\) inactivation gating variable in the dendrite | 14 |
| $m_{\infty,Na,dend,post} = \frac{1}{1 + \exp \left( - \frac{V_{dend,post} + 17}{11} \right)}$ | Steady-state value of postsynaptic Na\(^+\) activation gating variable in the dendrite | 14 |
| $\alpha_h,CalHVA,post = 0.000457 \exp \left( - \frac{V_{dend,post} + 13}{50} \right)$ | Transition rate of postsynaptic Ca\(_{LHVA}\) channel's inactivation gate from non-permissive to permissive state | 11,12 |
| $\alpha_m,CalHVA,post = -0.055 \exp \left( - \frac{V_{dend,post} + 27}{3.8} \right) - 1$ | Transition rate of postsynaptic Ca\(_{LHVA}\) channel's activation gate from non-permissive to permissive state | 11,12 |
| $\beta_h,CalHVA,post = \frac{0.0065 \exp \left( \frac{V_{dend,post} + 15}{28} \right)}{1 + \exp \left( \frac{V_{dend,post} + 15}{28} \right)}$ | Transition rate of postsynaptic Ca\(_{LHVA}\) channel's inactivation gate from permissive to non-permissive state | 11,12 |
| $\beta_m,CalHVA,post = 0.94 \exp \left( - \frac{V_{dend,post} + 75}{17} \right)$ | Transition rate of postsynaptic Ca\(_{LHVA}\) channel's activation gate from permissive to non-permissive state | 11,12 |
| $h_{\infty,CalHVA,dend,post} = \frac{\alpha_h,CalHVA,post}{\alpha_h,CalHVA,post + \beta_h,CalHVA,post}$ | Steady-state value of postsynaptic Ca\(_{LHVA}\) channel's inactivation gating variable in the dendrite | 11,12 |
| $m_{\infty,CalHVA,dend,post} = \frac{\alpha_m,CalHVA,post}{\alpha_m,CalHVA,post + \beta_m,CalHVA,post}$ | Steady-state value of postsynaptic Ca\(_{LHVA}\) channel's activation gating variable in the dendrite | 11,12 |
| $h_{\infty,CalLLVA,dend,post} = \frac{1}{1 + \exp \left( V_{dend,post} + 38+80 \right)}$ | Steady-state value of postsynaptic Ca\(_{LLVA}\) channel's inactivation gating variable in the dendrite | 13 |
| $m_{\infty,CalLLVA,dend,post} = \frac{1}{1 + \exp \left( - \frac{V_{dend,post} + 10+30}{6} \right)}$ | Steady-state value of postsynaptic Ca\(_{LLVA}\) channel's activation gating variable in the dendrite | 13 |
| $h_{\infty,IP3R,post} = \frac{K_{inh,post}}{[Ca^{2+}]_{post} + K_{inh,post}}$ | Steady-state value of postsynaptic IP\(_3\)R inactivation gating variable | 18,20 |
| $m_{\infty,IP3R,post} = \frac{[IP_3]_{post}}{K_{IP3,post} + [IP_3]_{post}}$ | Steady-state value of postsynaptic IP\(_3\)R activation gating variable | 18,20 |
| $n_{\infty,IP3R,post} = \frac{[Ca^{2+}]_{post}}{K_{act,post} + [Ca^{2+}]_{post}}$ | Steady-state value of postsynaptic IP\(_3\)R activation gating variable | 18,20 |
Table M. Intermediate variables of postsynaptic channel model in the dendrite.

| Intermediate variable | Description | Refs |
|-----------------------|-------------|------|
| \( B_{\text{NMDAR, post}} = \frac{1}{1 + \frac{M_{\text{ext, post}}}{3.579} \exp(-0.062 V_{\text{dend, post}})} \) | \( \text{Mg}^2+ \) block of postsynaptic NMDAR | 16 |
| \( \tau_{h, KA, \text{post}} = \frac{1}{3 \left( \frac{T_{ocelapse} - 23.5}{10} \right)} \left( \frac{\exp \left( \frac{V_{\text{dend, post}} + 238}{37} \right) + \exp \left( -\frac{V_{\text{dend, post}} + 46}{5} \right)}{19} \right) \) | Time constant for postsynaptic \( KA \) inactivation | 14, 54 |
| \( \tau_{m, KA, \text{post}} = \frac{1}{3 \left( \frac{T_{ocelapse} - 23.5}{10} \right)} \left( \frac{\exp \left( \frac{V_{\text{dend, post}} + 36}{20} \right) + \exp \left( -\frac{V_{\text{dend, post}} + 80}{13} \right) + 0.37}{19} \right) \) | Time constant for postsynaptic \( KA \) activation | 14 |
| \( \tau_{h, \text{CaLHVA, post}} = \frac{\alpha_{h, \text{CaLHVA, post}} + \beta_{h, \text{CaLHVA, post}}}{\alpha_{m, \text{CaLHVA, post}} + \beta_{m, \text{CaLHVA, post}}} \) | Time constant for postsynaptic \( Ca_{\text{LHVA}} \) inactivation | 11, 12 |
| \( \tau_{m, \text{CaLHVA, post}} = \frac{\alpha_{m, \text{CaLHVA, post}} + \beta_{m, \text{CaLHVA, post}}}{\alpha_{h, \text{CaLHVA, post}} + \beta_{h, \text{CaLHVA, post}}} \) | Time constant for postsynaptic \( Ca_{\text{LHVA}} \) activation | 11, 12 |
| \( \tau_{h, \text{CaLLVA, post}} = \frac{20 + \exp \left( \frac{V_{\text{dend, post}} + 10 + 40}{7} \right)}{1 + \exp \left( \frac{V_{\text{dend, post}} + 10 + 40}{7} \right)} \) | Time constant for postsynaptic \( Ca_{\text{LLVA}} \) inactivation | 13 |
| \( \tau_{m, \text{CaLLVA, post}} = \frac{5 + \exp \left( \frac{V_{\text{dend, post}} + 10 + 25}{5} \right)}{1 + \exp \left( \frac{V_{\text{dend, post}} + 10 + 25}{5} \right)} \) | Time constant for postsynaptic \( Ca_{\text{LLVA}} \) activation | 13 |
Table N. Postsynaptic channel and receptor currents.

| Intermediate variable | Description | Refs |
|-----------------------|-------------|------|
| \( I_{KDR,\text{soma,post}} = g_{KDR,\text{soma,post}} m_{KDR,\text{soma,post}}^2 (V_{\text{soma,post}} - V_{K,\text{post}}) \) | Postsynaptic \( K_{DR} \) current density in the soma | 14 |
| \( I_{L,\text{soma,post}} = g_{L,\text{soma,post}} (V_{\text{soma,post}} - V_{L,\text{post}}) \) | Postsynaptic leak current density in the soma | 14 |
| \( I_{Na,\text{soma,post}} = g_{Na,\text{soma,post}} m_{Na,\text{soma,post}}^2 h_{Na,\text{soma,post}} (V_{\text{soma,post}} - V_{Na,\text{soma,post}}) \) | Postsynaptic \( Na^+ \) current density in the soma | 14 |
| \( I_{NaP,\text{soma,post}} = g_{NaP,\text{soma,post}} n_{\infty,NaP,\text{soma,post}} (V_{\text{soma,post}} - V_{Na,\text{soma,post}}) \) | Postsynaptic \( NaP \) current density in the soma | 14 |
| \( I_{K,\text{dend,post}} = g_{K,\text{dend,post}} m_{K,\text{dend,post}}^4 h_{K,\text{dend,post}} (V_{\text{dend,post}} - V_{K,\text{post}}) \) | Postsynaptic \( K_A \) current density in the dendrite | 14 |
| \( I_{CaLLVA,\text{dend,post}} = g_{CaLLVA,\text{dend,post}} m_{CaLLVA,\text{dend,post}}^2 h_{CaLLVA,\text{dend,post}} (V_{\text{dend,post}} - V_{Ca,\text{post}}) \) | Postsynaptic \( Ca_{LLVA} \) current density in the dendrite | 11, 12 |
| \( I_{CaLHVA,\text{dend,post}} = g_{CaLHVA,\text{dend,post}} m_{CaLHVA,\text{dend,post}}^2 h_{CaLHVA,\text{dend,post}} (V_{\text{dend,post}} - V_{Ca,\text{post}}) \) | Postsynaptic \( Ca_{LHVA} \) current density in the dendrite | 13 |
| \( I_{L,\text{dend,post}} = g_{L,\text{dend,post}} (V_{\text{dend,post}} - V_{L,\text{post}}) \) | Postsynaptic leak current density in the dendrite | 14 |
| \( I_{Na,\text{dend,post}} = g_{Na,\text{dend,post}} m_{Na,\text{dend,post}}^2 h_{Na,\text{dend,post}} (V_{\text{dend,post}} - V_{Na,\text{dend,post}}) \) | Postsynaptic \( Na^+ \) current density in the dendrite | 14 |
| \( I_{AMPAR,\text{post}} = g_{AMPAR,\text{post}} m_{AMPAR,\text{post}} (V_{\text{dend,post}} - V_{AMPAR,\text{post}}) \) | Postsynaptic AMPAR current density in the dendrite | 16 |
| \( I_{Ca,NMDAR,\text{post}} = g_{NMDAR,\text{post}} B_{NMDAR,\text{post}} m_{NMDAR,\text{post}} (V_{\text{dend,post}} - V_{NMDAR,\text{post}}) \) | \( Ca^{2+} \) current density via postsynaptic NMDARs in the dendrite | 16 |
| \( I_{\text{coupl,dend,post}} = \frac{g_{\text{coupl,post}}}{1 - p_{\text{post}}} (V_{\text{soma,post}} - V_{\text{dend,post}}) \) | Postsynaptic current coupling term in the dendrite | 14 |
| \( I_{\text{coupl,soma,post}} = \frac{g_{\text{coupl,post}}}{p_{\text{post}}} (V_{\text{dend,post}} - V_{\text{soma,post}}) \) | Postsynaptic current coupling term in the soma | 14 |
Table O. Intermediate variables of postsynaptic flux model.

| Intermediate variable | Description                                                                 | Refs |
|-----------------------|-----------------------------------------------------------------------------|------|
| $J_{\text{CaL,post}} = -\frac{I_{\text{CaLHVA,dend,post}} + I_{\text{CaLLVA,dend,post}}}{c_{\text{Ca,post}}}$ | $\text{Ca}^{2+}$ flux via postsynaptic $\text{Ca}_{\text{LHVA}}$ and $\text{Ca}_{\text{LLVA}}$ channels |      |
| $J_{\text{IP3R,post}} = v_{\text{IP3R,post}} m_{\infty,\text{IP3R,post}} \frac{n_{\infty,\text{IP3R,post}}}{n_{\text{IP3R,post}}} \left([\text{Ca}^{2+}]_{\text{ER,post}} - [\text{Ca}^{2+}]_{\text{post}}\right)$ | $\text{Ca}^{2+}$ flux via postsynaptic IP$_{3}$R | 18 20 |
| $J_{\text{leakER,post}} = r_{\text{leakER,post}} \left([\text{Ca}^{2+}]_{\text{ER,post}} - [\text{Ca}^{2+}]_{\text{post}}\right)$ | Postsynaptic Ca$^{2+}$ leak flux from ER to cytosol | 18 19 |
| $J_{\text{leakCell,post}} = r_{\text{leakCell,post}} \left([\text{Ca}^{2+}]_{\text{ext,post}} - [\text{Ca}^{2+}]_{\text{post}}\right)$ | Postsynaptic Ca$^{2+}$ leak flux from extracellular space to cytosol | 21 |
| $J_{\text{NMDAR,post}} = -\frac{I_{\text{Ca,NMDAR,post}}}{c_{\text{Ca,post}}}$ | $\text{Ca}^{2+}$ flux via postsynaptic NMDAR |      |
| $J_{\text{PMCA,post}} = \frac{k_{\text{Ca,post}} A_{\text{spine,post}} v_{\text{PMCA,post}}}{V_{\text{spine,post}}} \frac{[\text{Ca}^{2+}]_{\text{post}}^2}{K_{\text{PMCA,post}}^2 + [\text{Ca}^{2+}]_{\text{post}}^2}$ | $\text{Ca}^{2+}$ flux via postsynaptic PMCA pump | 21 |
| $J_{\text{SERCA,post}} = v_{\text{SERCA,post}} \frac{[\text{Ca}^{2+}]_{\text{post}}^2}{K_{\text{SERCA,post}}^2 + [\text{Ca}^{2+}]_{\text{post}}^2}$ | $\text{Ca}^{2+}$ flux via postsynaptic SERCA pump | 18 19 |
Table P. Reactions of postsynaptic neuron model.

| Reaction | Description | Refs |
|----------|-------------|------|
| Glu\textsubscript{synleft} → ∅ | Postsynaptic mGluR Glu uptake | 17 |
| Glu\textsubscript{synleft} + mGluR ⇌ Glu\textsubscript{mGluR} | Postsynaptic mGluR Glu binding | 17 |
| Glu\textsubscript{mGluR} ⇌ Glu\textsubscript{mGluRdesens} | Postsynaptic mGluR desensitization | 17 |
| Gαβγ + Glu\textsubscript{mGluR} ⇌ Gαβγ\textsubscript{Glu} | Postsynaptic G protein activation | 17 |
| Ca\textsuperscript{2+} + PLC ⇌ Ca\textsubscript{PLC} | Postsynaptic PLC binding Ca\textsuperscript{2+} first | 17 |
| GαGTP + Ca\textsubscript{PLC} ⇌ Ca\textsubscript{GαGTP}\textsubscript{PLC} | Postsynaptic PLC binding GαGTP second | 17 |
| GαGTP + PLC ⇌ GαGTP\textsubscript{PLC} | Postsynaptic PLC binding GαGTP first | 17 |
| Ca\textsuperscript{2+} + GαGTP\textsubscript{PLC} ⇌ Ca\textsubscript{GαGTP}\textsubscript{PLC} | Postsynaptic PLC binding Ca\textsuperscript{2+} second | 17 |
| PIP\textsubscript{2} + Ca\textsubscript{PLC} ⇌ Ca\textsubscript{PIP}\textsubscript{2}\textsubscript{PLC} + Ca\textsubscript{DAG}\textsubscript{PLC} + IP\textsubscript{3} | Postsynaptic DAG production, step 1 | 17 |
| Ca\textsubscript{DAG}\textsubscript{PLC} → Ca\textsubscript{PLC} + DAG | Postsynaptic DAG production, step 2 | 17 |
| PIP\textsubscript{2} + Ca\textsubscript{GαGTP}\textsubscript{PLC} ⇌ Ca\textsubscript{GαGTP}\textsubscript{PIP}\textsubscript{2}\textsubscript{PLC} → Ca\textsubscript{DAG}\textsubscript{GαGTP}\textsubscript{PLC} + IP\textsubscript{3} | Postsynaptic DAG production, step 1 | 17 |
| Ca\textsubscript{DAG}\textsubscript{GαGTP}\textsubscript{PLC} → Ca\textsubscript{GαGTP}\textsubscript{PLC} + DAG | Postsynaptic DAG production, step 2 | 17 |
| IP\textsubscript{3} → IP\textsubscript{3deg} | Postsynaptic IP\textsubscript{3} degradation | 17 |
| IP\textsubscript{3deg} + PIKin ⇌ IP\textsubscript{3deg}\textsubscript{PIKin} → PIP\textsubscript{2} + PIKin | Postsynaptic PIP\textsubscript{2} regeneration by PIKin | 17 |
| GαGTP\textsubscript{PLC} → PLC + GαGDP | Postsynaptic GAP activity on PLC | 17 |
| Ca\textsubscript{GαGTP}\textsubscript{PLC} → Ca\textsubscript{PLC} + GαGDP | Postsynaptic GAP activity on PLC | 17 |
| GαGTP → GαGDP | Postsynaptic GαGTP hydrolysis | 17 |
| GαGDP → Gαβγ | Postsynaptic G protein regeneration | 17 |
| Ca\textsuperscript{2+} + DAGL ⇌ Ca\textsubscript{DAGL} | Postsynaptic Ca\textsuperscript{2+} activating DAGL | 17 |
| DAG + Ca\textsubscript{DAGL} ⇌ Ca\textsubscript{DAG}\textsubscript{DAGL} → Ca\textsubscript{DAGL} + 2-AG | Postsynaptic 2-AG production | 17 |
| 2-AG → ∅ | Postsynaptic 2-AG degradation | 17 |
| DAG → ∅ | Postsynaptic DAG degradation | 22 |
Table Q. Reaction rates of postsynaptic model.

| Reaction rate | Description | Refs |
|---------------|-------------|------|
| \( v_{\text{Glu,f,post}} = k_{\text{Glu,f,post}} (1 - f_{\text{Glu,pre}}) [\text{Glu}]_{\text{syncl}} \) | Reaction rate for postsynaptic mGluR Glu uptake | Mod. from 17 |
| \( v_{\text{mGluR,f,post}} = k_{\text{mGluR,f,post}} (1 - f_{\text{pre,post}}) [\text{Glu}]_{\text{syncl}} [\text{mGluR}]_{\text{post}} \) | Reaction rates of Glu binding and unbinding to postsynaptic mGluR | Mod. from 17 |
| \( v_{\text{mGluR,b,post}} = k_{\text{mGluR,b,post}} [\text{Glu}]_{\text{syncl}} [\text{mGluR}]_{\text{post}} \) | Reaction rates into and out of desensitized state of postsynaptic mGluR | 17 |
| \( v_{\text{Gact,f,post}} = k_{\text{Gact,f,post}} [\text{G} \alpha \beta \gamma]_{\text{post}} [\text{Glu}]_{\text{syncl}} [\text{mGluR}]_{\text{post}} \) | Reaction rates of postsynaptic G protein activation and inactivation | 17 |
| \( v_{\text{Gact,b,post}} = k_{\text{Gact,b,post}} [\text{G} \alpha \beta \gamma]_{\text{post}} [\text{Glu}]_{\text{syncl}} [\text{mGluR}]_{\text{post}} \) | | 17 |
| \( v_{\text{Ca}_{\text{PLC1,f,post}} = k_{\text{Ca}_{\text{PLC1,f,post}}} [\text{Ca}^{2+}]_{\text{post}} [\text{PLC}]_{\text{post}} \) | Reaction rates of postsynaptic PLC binding and unbinding Ca\(^{2+}\) first | 17 |
| \( v_{\text{Ca}_{\text{PLC1,b,post}} = k_{\text{Ca}_{\text{PLC1,b,post}}} [\text{Ca}]_{\text{PLC}}_{\text{post}} \) | Reaction rates of postsynaptic PLC binding and unbinding GTP second | 17 |
| \( v_{\text{PLC2,f,post}} = k_{\text{PLC2,f,post}} [\text{G} \alpha \beta \gamma]_{\text{post}} [\text{Ca}]_{\text{PLC}}_{\text{post}} \) | Reaction rates of postsynaptic PLC binding and unbinding GTP first | 17 |
| \( v_{\text{PLC1,b,post}} = k_{\text{PLC1,b,post}} [\text{Ca}]_{\text{PLC}}_{\text{post}} \) | Reaction rates of postsynaptic PLC binding and unbinding Ca\(^{2+}\) second | 17 |
| \( v_{\text{Ca}_{\text{PLC2,f,post}} = k_{\text{Ca}_{\text{PLC2,f,post}}} [\text{Ca}]_{\text{PLC}}_{\text{post}} \) | Reaction rates of postsynaptic DAG production, step 1 | 17 |
| \( v_{\text{Ca}_{\text{PLC2,b,post}} = k_{\text{Ca}_{\text{PLC2,b,post}}} [\text{Ca}]_{\text{PLC}}_{\text{post}} \) | Reaction rates of postsynaptic DAG production, step 2 | 17 |
| \( v_{\text{DAG1,f,post}} = k_{\text{DAG1,f,post}} [\text{IP}_3]_{\text{post}} [\text{Ca}]_{\text{PLC}}_{\text{post}} \) | Reaction rates of postsynaptic DAG production, step 1 | 17 |
| \( v_{\text{DAG1,b,post}} = k_{\text{DAG1,b,post}} [\text{Ca}]_{\text{PLC}}_{\text{post}} \) | Reaction rates of postsynaptic DAG production, step 1 | 17 |
| \( v_{\text{DAG1,c,post}} = k_{\text{DAG1,c,post}} [\text{Ca}]_{\text{PLC}}_{\text{post}} \) | Reaction rates of postsynaptic DAG production, step 1 | 17 |
| \( v_{\text{DAG2,f,post}} = k_{\text{DAG2,f,post}} [\text{Ca}]_{\text{DAG}_2}_{\text{post}} \) | Reaction rates of postsynaptic DAG production, step 2 | 17 |
| \( v_{\text{DAG3,f,post}} = k_{\text{DAG3,f,post}} [\text{Ca}]_{\text{GTP}}_{\text{PLC}}_{\text{post}} \) | Reaction rates of postsynaptic DAG production, step 1 | 17 |
| \( v_{\text{DAG3,b,post}} = k_{\text{DAG3,b,post}} [\text{Ca}]_{\text{GTP}}_{\text{PLC}}_{\text{post}} \) | Reaction rates of postsynaptic DAG production, step 1 | 17 |
| \( v_{\text{DAG3,c,post}} = k_{\text{DAG3,c,post}} [\text{Ca}]_{\text{GTP}}_{\text{PLC}}_{\text{post}} \) | Reaction rates of postsynaptic DAG production, step 1 | 17 |
| \( v_{\text{DAG4,f,post}} = k_{\text{DAG4,f,post}} [\text{Ca}]_{\text{DAG}_2}_{\text{GTP}_{\text{PLC}}}_{\text{post}} \) | Reaction rates of postsynaptic DAG production, step 2 | 17 |
| \( v_{\text{degIP3,post}} = k_{\text{degIP3,post}} [\text{IP}_3]_{\text{post}} \) | Reaction rate of postsynaptic IP\(_3\) degradation | 17 |
| \( v_{\text{PPI2,f,post}} = k_{\text{PPI2,f,post}} [\text{PPI2}_\text{deg}]_{\text{post}} [\text{PIKin}]_{\text{post}} \) | Reaction rates of postsynaptic PIP\(_2\) regeneration by PIKin | 17 |
| \( v_{\text{PPI2,b,post}} = k_{\text{PPI2,b,post}} [\text{PPI2}_\text{deg}]_{\text{post}} [\text{PIKin}]_{\text{post}} \) | Reaction rates of postsynaptic PIP\(_2\) regeneration by PIKin | 17 |
| \( v_{\text{PPI2,c,post}} = k_{\text{PPI2,c,post}} [\text{PPI2}_\text{deg}]_{\text{post}} [\text{PIKin}]_{\text{post}} \) | Reaction rates of postsynaptic PIP\(_2\) regeneration by PIKin | 17 |
| \( v_{\text{GAP1,f,post}} = k_{\text{GAP1,f,post}} [\text{Ga}]_{\text{GTP}}_{\text{PLC}}_{\text{post}} \) | Reaction rate of postsynaptic GAP activity on PLC | 17 |
| \( v_{\text{GAP2,f,post}} = k_{\text{GAP2,f,post}} [\text{Ca}]_{\text{GaGTP}}_{\text{PLC}}_{\text{post}} \) | Reaction rate of postsynaptic GAP activity on PLC | 17 |
| \( v_{\text{hydroG,f,post}} = k_{\text{hydroG,f,post}} [\text{Ga}]_{\text{GTP}}_{\text{post}} \) | Reaction rate of postsynaptic GaGTP hydrolysis | 17 |
| \( v_{\text{regenG,f,post}} = k_{\text{regenG,f,post}} [\text{Ga}]_{\text{GDP}}_{\text{post}} \) | Reaction rate of postsynaptic G protein regeneration | 17 |
| \( v_{\text{DAGL,f,post}} = k_{\text{DAGL,f,post}} [\text{Ca}]_{\text{Ca}}_{\text{DAGL}}_{\text{post}} \) | Reaction rates of postsynaptic Ca\(^{2+}\) activation of DAGL | 17 |
| \( v_{\text{DAGL,b,post}} = k_{\text{DAGL,b,post}} [\text{Ca}]_{\text{Ca}}_{\text{DAGL}}_{\text{post}} \) | Reaction rates of postsynaptic Ca\(^{2+}\) activation of DAGL | 17 |
| \( v_{\text{prodAG,f,post}} = k_{\text{prodAG,f,post}} [\text{DAG}]_{\text{post}} [\text{Ca}]_{\text{DAGL}}_{\text{post}} \) | Reaction rates of postsynaptic 2-AG production | 17 |
| \( v_{\text{prodAG,b,post}} = k_{\text{prodAG,b,post}} [\text{Ca}]_{\text{DAGL}}_{\text{post}} \) | Reaction rates of postsynaptic 2-AG production | 17 |
| \( v_{\text{degAG,c,post}} = k_{\text{degAG,c,post}} [\text{Ca}]_{\text{DAGL}}_{\text{post}} \) | Reaction rates of postsynaptic DAG degradation | 17 |
| \( v_{\text{degDAG,post}} = k_{\text{degDAG,post}} [\text{DAG}]_{\text{post}} \) | Reaction rates of postsynaptic DAG degradation | 22 |
| Parameter | Value | Unit | Description | Refs |
|-----------|-------|------|-------------|------|
| $\alpha_{\text{AMPAR,post}}$ | 0.0011 | $\frac{1}{\mu\text{m} \cdot \text{ms}}$ | Rate constant of opening postsynaptic AMPAR | 16 |
| $\alpha_{\text{NMDAR,post}}$ | $7.2 \times 10^{-5}$ | $\frac{1}{\mu\text{m} \cdot \text{ms}}$ | Rate constant of opening postsynaptic NMDAR | 16 |
| $\beta_{\text{AMPAR,post}}$ | 0.19 | $\frac{1}{\text{ms}}$ | Rate constant of closing postsynaptic AMPAR | 16 |
| $\beta_{\text{NMDAR,post}}$ | 0.0066 | $\frac{1}{\text{ms}}$ | Rate constant of closing postsynaptic NMDAR | 16 |
| $C_{\text{m,post}}$ | 3 | $\mu\text{F/cm}^2$ | Postsynaptic membrane capacitance per unit area | 16: 2.7 $\mu\text{F/cm}^2$ |
| $g_{\text{AMPAR,post}}$ | 0.1 | $\text{mS/cm}^2$ | Maximum conductance of postsynaptic AMPAR per unit area | 16: 55, 56: $3.5 \times 10^{-7} \text{ mS}$ |
| $g_{c,\text{post}}$ | 2.1 | $\text{mS/cm}^2$ | Coupling conductance between postsynaptic soma and dendrite per unit area | 15 |
| $g_{\text{CaLHVA,dend,post}}$ | 0.23 | $\text{mS/cm}^2$ | Maximum conductance of postsynaptic $\text{Ca}_{\text{LHVA}}$ current in the dendrite per unit area | 11: 0.01 $\text{mS/cm}^2$ |
| $g_{\text{CaLLVA,dend,post}}$ | 0.23 | $\text{mS/cm}^2$ | Maximum conductance of postsynaptic $\text{Ca}_{\text{LLVA}}$ current in the dendrite per unit area | 13: 0.01 $\text{mS/cm}^2$ |
| $g_{\text{K,dend,post}}$ | 1 | $\text{mS/cm}^2$ | Maximum conductance of postsynaptic $\text{K}_{\text{A}}$ current in the dendrite per unit area | Mod. from 14 |
| $g_{\text{KDR,soma,post}}$ | 50 | $\text{mS/cm}^2$ | Maximum conductance of postsynaptic $\text{K}_{\text{DR}}$ current in the soma per unit area | 14: 154 $\text{mS/cm}^2$ |
| $g_{l,dend,post}$ | 0.2 | $\text{mS/cm}^2$ | Leak conductance of postsynaptic dendrite per unit area | 15: 0.1 $\text{mS/cm}^2$ |
| $g_{l,soma,post}$ | 0.2 | $\text{mS/cm}^2$ | Leak conductance of postsynaptic soma per unit area | 14: 0.222 $\text{mS/cm}^2$ |
| $g_{\text{Na,dend,post}}$ | 0.06 | $\text{mS/cm}^2$ | Maximum conductance of postsynaptic $\text{Na}^+$ current in the dendrite per unit area | 14: 1.78 $\text{mS/cm}^2$ |
| $g_{\text{Na,soma,post}}$ | 60 | $\text{mS/cm}^2$ | Maximum conductance of postsynaptic $\text{Na}^+$ current in the soma per unit area | 14: 178 $\text{mS/cm}^2$ |
| $g_{\text{NaP,soma,post}}$ | 0.1 | $\text{mS/cm}^2$ | Maximum conductance of postsynaptic $\text{Na}_{\text{P}}$ current in the soma per unit area | 14: 0.6 $\text{mS/cm}^2$ |
| $g_{\text{NMDAR,post}}$ | 0.001 | $\text{mS/cm}^2$ | Maximum conductance of postsynaptic NMDAR per unit area | 16: $10^{-8} \text{ mS}$ |
| $M_{\text{ext,post}}$ | 1,000 | $\mu\text{M}$ | $\text{Mg}^{2+}$ concentration outside postsynaptic neuron | 16 |
| $p_{\text{post}}$ | 0.5 | 1 | Proportion of postsynaptic cell area taken by soma | 15 |
| $t_{h,\text{Na,post}}$ | 0.5 | $\text{ms}$ | Time constant for postsynaptic $\text{Na}^+$ inactivation | 14 |
| $t_{m,\text{KDR,post}}$ | 2 | $\text{ms}$ | Time constant for postsynaptic $\text{K}_{\text{DR}}$ activation | 14 |
| $t_{m,\text{Na,post}}$ | 0.05 | $\text{ms}$ | Time constant for postsynaptic $\text{Na}^+$ activation | 14 |
| $V_{\text{AMPAR,post}}$ | 0 | $\text{mV}$ | Reversal potential of postsynaptic AMPAR current | 16 |
| $V_{\text{Ca,post}}$ | 90 | $\text{mV}$ | Reversal potential of postsynaptic $\text{Ca}_{\text{LHVA}}$ and $\text{Ca}_{\text{LLVA}}$ currents | 11 |
| $V_{\text{K,post}}$ | $-85$ | $\text{mV}$ | Reversal potential of postsynaptic $\text{K}^+$ current | 14: $-77 \text{ mV}$ |
| $V_{\text{L,post}}$ | $-70$ | $\text{mV}$ | Leak reversal potential of postsynaptic neuron | 14: $-73.6 \text{ mV}$ |
| $V_{\text{Na,dend,post}}$ | 50 | $\text{mV}$ | Reversal potential of postsynaptic $\text{Na}^+$ current in the dendrite | 14 |
| $V_{\text{Na,soma,post}}$ | 50 | $\text{mV}$ | Reversal potential of postsynaptic $\text{Na}^+$ current in the soma | 14: 90 $\text{ mV}$ |
| $V_{\text{NMDAR,post}}$ | 0 | $\text{mV}$ | Reversal potential of postsynaptic NMDAR current | 16 |
Table S. Parameter values of postsynaptic flux model.

| Parameter                  | Value                        | Unit            | Description                                                                 | Refs  |
|----------------------------|------------------------------|-----------------|-----------------------------------------------------------------------------|-------|
| $A_{\text{spine,post}}$    | $4\pi r_{\text{spine,post}}^2$ | cm$^2$          | Postsynaptic surface area of dendritic spine                               |       |
| $B_{\text{post}}$          | 0.5                          | 1               | Postsynaptic fast buffering factor                                          | 22 : 0.01 |
| $c_{\text{Ca,post}}$       | $eF V_{\text{spine,post}} / B_{\text{post}} A_{\text{spine,post}}$ | µA ms cm$^2$ µM | Postsynaptic scaling factor to convert from units µA cm$^2$ to µM ms       | 22    |
| $C_{\text{ext,post}}$      | 2.015.1                      | µM              | Ca$^{2+}$ concentration outside postsynaptic neuron                        | 17    |
| $k_{\text{Ca,post}}$       | 1.000                        | 1               | Postsynaptic scaling factor to convert from units mM ms to µM ms           |       |
| $k_{\text{act,post}}$      | 0.8                          | µM              | Postsynaptic IP$_3$R dissociation constant of Ca$^{2+}$ (activation)       | 20    |
| $k_{\text{inh,post}}$      | 1.9                          | µM              | Postsynaptic IP$_3$R dissociation constant of Ca$^{2+}$ (inhibition)       | 20    |
| $K_{\text{IP3,post}}$      | 0.15                         | µM              | Postsynaptic IP$_3$R dissociation constant of IP$_3$ (activation)          | 20    |
| $K_{\text{PMCA,post}}$     | 0.12                         | µM              | Half-activation constant of postsynaptic PMCA pump                          | 57    |
| $K_{\text{SERCA,post}}$    | 0.4                          | µM              | Half-activation constant of postsynaptic SERCA pump                         | 20    |
| $r_{\text{ER,post}}$       | 0.185                        | 1               | Ratio between postsynaptic ER and cytosol volumes                           | 18    |
| $r_{\text{leak,Cell,post}}$| $J_{\text{PMCA,post}} - J_{\text{Ca,post}} - J_{\text{NMDAR,post}} / C_{\text{ext,post}} - [Ca^{2+}]_{\text{post}}$ | 1 ms           | Postsynaptic leak parameter over cell membrane calculated at resting concentrations |       |
| $r_{\text{leak,ER,post}}$  | $J_{\text{SERCA,post}} - J_{\text{IP3R,post}} / [Ca^{2+}]_{\text{ER,post}} - [Ca^{2+}]_{\text{post}}$ | 1 ms           | Postsynaptic ER leak parameter calculated at resting concentrations         |       |
| $r_{\text{spine,post}}$    | $5 \times 10^{-5}$          | cm              | Postsynaptic radius of dendritic spine                                      | 58    |
| $\tau_{\text{IP3R,post}}$ | 2.000                        | ms              | Time constant for postsynaptic IP$_3$R inactivation                         | 20    |
| $v_{\text{IP3R,post}}$     | 0.01                         | 1 ms            | Maximum rate of Ca$^{2+}$ release via postsynaptic IP$_3$R                  | 20 : 0.0085 1 ms |
| $v_{\text{PMCA,post}}$     | $8 \times 10^{-11}$         | µMol ms$^{-2}$  | Maximum rate of Ca$^{2+}$ uptake by postsynaptic PMCA pump per unit area    | 21 : 10$^{-9}$ µMol ms$^{-2}$ |
| $v_{\text{SERCA,post}}$    | 0.003                        | µM ms           | Maximum rate of Ca$^{2+}$ uptake by postsynaptic SERCA pump                 | 18 : 0.0009 µM ms |
| $V_{\text{spine,post}}$    | $\frac{4}{3} \pi r_{\text{spine,post}}^3$ | cm$^3$          | Postsynaptic volume of dendritic spine                                      |       |
### Table T. Parameter values of postsynaptic reaction model.

| Parameter         | Value   | Unit   | Refs | Parameter         | Value   | Unit   | Refs | Parameter         | Value   | Unit   | Refs |
|-------------------|---------|--------|------|-------------------|---------|--------|------|-------------------|---------|--------|------|
| $k_{\text{Glu,f,post}}$ | 0.2     | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{mGluR,f,post}}$ | 0.0001  | $\frac{1}{\text{mM ms}}$ | 17   | $k_{\text{mGluR,b,post}}$ | 0.01    | $\frac{1}{\text{ms}}$ | 17   |
| $k_{\text{mGluRdes,f,post}}$ | 0.00025 | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{mGluRdes,b,post}}$ | $10^{-6}$ | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{Gact,f,post}}$ | 0.015   | $\frac{1}{\text{mM ms}}$ | 17   |
| $k_{\text{Gact,b,post}}$ | 0.0072  | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{Gact,c,post}}$ | 0.0005  | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{Ca,PLC1,f,post}}$ | 0.002   | $\frac{1}{\text{mM ms}}$ | 17   |
| $k_{\text{Ca,PLC1,b,post}}$ | 0.12    | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{G,post}}$ | 0.015   | $\frac{1}{\text{mM ms}}$ | 17   | $k_{\text{G,post}}$ | 0.01    | $\frac{1}{\text{ms}}$ | 17   |
| $k_{\text{G,post}}$ | 0.012   | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{Ca,PLC2,b,post}}$ | 0.04    | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{Ca,PLC2,b,post}}$ | 0.08    | $\frac{1}{\text{mM ms}}$ | 17   |
| $k_{\text{DAG1,f,post}}$ | 0.0006  | $\frac{1}{\text{mM ms}}$ | 17   | $k_{\text{DAG1,b,post}}$ | 0.01    | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{DAG1,c,post}}$ | 0.025   | $\frac{1}{\text{ms}}$ | 17   |
| $k_{\text{DAG2,f,post}}$ | 0.2     | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{DAG3,b,post}}$ | 0.075   | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{DAG3,c,post}}$ | 0.25    | $\frac{1}{\text{ms}}$ | 17   |
| $k_{\text{DAG3,f,post}}$ | 0.015   | $\frac{1}{\text{mM ms}}$ | 17   | $k_{\text{DAG3,b,post}}$ | 0.001   | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{DAG3,c,post}}$ | 0.001   | $\frac{1}{\text{ms}}$ | 17   |
| $k_{\text{DAG4,f,post}}$ | 1       | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{DAG4,b,post}}$ | 0.002   | $\frac{1}{\text{mM ms}}$ | 17   | $k_{\text{DAG4,b,post}}$ | 0.03    | $\frac{1}{\text{ms}}$ | 17   |
| $k_{\text{degIP3,post}}$ | 0.03    | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{degIP3,post}}$ | 0.03    | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{degGAP1,post}}$ | 0.001   | $\frac{1}{\text{ms}}$ | 17   |
| $k_{\text{degGAP1,post}}$ | 0.03    | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{degGAP2,post}}$ | 0.001   | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{degGAP2,post}}$ | 0.01    | $\frac{1}{\text{ms}}$ | 17   |
| $k_{\text{degGAP2,post}}$ | 0.125   | $\frac{1}{\text{mM ms}}$ | 17   | $k_{\text{DAGL,b,post}}$ | 0.05    | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{DAGL,post}}$ | 0.0025  | $\frac{1}{\text{mM ms}}$ | 17   |
| $k_{\text{degAG,post}}$ | 0.005   | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{prodAG,b,post}}$ | 0.0015  | $\frac{1}{\text{ms}}$ | 17   | $k_{\text{prodAG,c,post}}$ | 0.001   | $\frac{1}{\text{ms}}$ | 17   |
| $k_{\text{degDAG,post}}$ | 0.00066 | $\frac{1}{\text{ms}}$ | 22    | $k_{\text{degDAG,post}}$ | 0.57    | $\frac{1}{\text{ms}}$ | 17   |
Table U. Initial values of postsynaptic variables.

| Variable                  | Initial value | Unit | Description                                               | Refs |
|---------------------------|---------------|------|-----------------------------------------------------------|------|
| [2-AG]_{post}             | 0.0010453     | µM   | Postsynaptic 2-AG concentration                           |      |
| [Ca^{2+}]_{post}          | 0.049978      | µM   | Postsynaptic Ca^{2+} concentration                        |      |
| [Ca^{2+}]_{ER,post}       | 62.9016       | µM   | Postsynaptic Ca^{2+} concentration in ER                  |      |
| [Ca_{DAG,DAGL}]_{post}    | 0.0052265     | µM   | Concentration of postsynaptic Ca^{2+}-DAG-DAGL complex    |      |
| [Ca_{DAG, GaGTP, PLC}]_{post} | 0            | µM   | Concentration of postsynaptic Ca^{2+}-DAG-GaGTP-PLC complex |      |
| [Ca_{DAG, PLC}]_{post}    | 8.8541 × 10^{-5} | µM | Concentration of postsynaptic Ca^{2+}-DAG-PLC complex     |      |
| [Ca_{DAGL}]_{post}        | 0.27637       | µM   | Postsynaptic Ca^{2+}-DAGL complex                         |      |
| [Ca_{GaGTP,PIP2, PLC}]_{post} | 0            | µM | Concentration of postsynaptic Ca^{2+}-GaGTP-PIP_{2}-PLC complex |      |
| [Ca_{GaGTP, PLC}]_{post}  | 0             | µM   | Concentration of postsynaptic Ca^{2+}-GaGTP-PLC complex   |      |
| [Ca_{PIP2, PLC}]_{post}   | 0.00070833    | µM   | Concentration of postsynaptic Ca^{2+}-PIP_{2}-PLC complex |      |
| [Ca_{PLC}]_{post}         | 0.00083161    | µM   | Concentration of postsynaptic Ca^{2+}-PLC complex         |      |
| [DAG]_{post}              | 0.018912      | µM   | Postsynaptic DAG concentration                           |      |
| [DAGL]_{post}             | 2.2119        | µM   | Postsynaptic DAGL concentration                           |      |
| [Gaβγ]_{post}             | 3.5           | µM   | Postsynaptic Gaβγ concentration                           |      |
| [Gaβγ,Glu, mGluR]_{post}  | 0             | µM   | Concentration of postsynaptic Gaβγ-Glu-mGluR complex      |      |
| [GaGDP]_{post}            | 0             | µM   | Postsynaptic GaGDP concentration                          |      |
| [GaGTP]_{post}            | 0             | µM   | Postsynaptic GaGTP concentration                          |      |
| [GaGTP, PLC]_{post}       | 0             | µM   | Concentration of postsynaptic GaGTP-PLC complex           |      |
| [Glu, mGluR]_{post}       | 0             | µM   | Concentration of postsynaptic Glu-mGluR complex           |      |
| [Glu, mGluRdesens]_{post} | 0             | µM   | Concentration of postsynaptic Glu-mGluRdesens complex     |      |
| [IP_{3}]_{post}           | 0.0017708     | µM   | Postsynaptic IP_{3} concentration                         |      |
| [IP_{3deg}]_{post}        | 0.014141      | µM   | Postsynaptic IP_{3deg} concentration                      |      |
| [IP_{3deg, PIKin}]_{post} | 0.017708      | µM   | Concentration of postsynaptic IP_{3deg, PIKin} complex    |      |
| [mGluR]_{post}            | 5             | µM   | Postsynaptic mGluR concentration                          |      |
| [PIKin]_{post}            | 1.2523        | µM   | Postsynaptic PIKin concentration                          |      |
| [PIP_{2}]_{post}          | 49.6857       | µM   | Postsynaptic PIP_{2} concentration                        |      |
| [PLC]_{post}              | 0.99837       | µM   | Postsynaptic PLC concentration                            |      |
| V_{dend, post}            | −68.1916      | mV   | Postsynaptic membrane potential in the dendrite           |      |
| V_{soma, post}            | −68.1057      | mV   | Postsynaptic membrane potential in the soma               |      |
### Table V. Initial values of postsynaptic variables.

| Variable                      | Initial value | Unit | Description                                                                 | Refs |
|-------------------------------|---------------|------|------------------------------------------------------------------------------|------|
| $h_{CaLHVA, dend, post}$      | $h_{\infty, CaLHVA, dend, post}$ | 1    | Gating variable for postsynaptic CaLHVA inactivation in the dendrite         | [18,19] |
| $h_{CaLLVA, dend, post}$      | $h_{\infty, CaLLVA, dend, post}$ | 1    | Gating variable for postsynaptic CaLLVA inactivation in the dendrite         | [18,19] |
| $h_{IP3R, post}$              | $h_{\infty, IP3R, post}$ | 1    | Gating variable for postsynaptic IP$_3$R inactivation                       | [18,19] |
| $h_{KA, dend, post}$          | $h_{\infty, KA, dend, post}$ | 1    | Gating variable for postsynaptic $K_A$ inactivation in the dendrite          | [18,19] |
| $h_{Na, dend, post}$          | $h_{\infty, Na, dend, post}$ | 1    | Gating variable for postsynaptic $Na^+$ inactivation in the dendrite         | [18,19] |
| $h_{Na, soma, post}$          | $h_{\infty, Na, soma, post}$ | 1    | Gating variable for postsynaptic $Na^+$ inactivation in the soma             | [18,19] |
| $m_{AMPA, post}$              | $m_{\infty, AMPA, post}$ | 1    | Fraction of postsynaptic AMPARs in open state                               | [18,19] |
| $m_{CaLHVA, dend, post}$      | $m_{\infty, CaLHVA, dend, post}$ | 1    | Gating variable for postsynaptic CaLHVA activation in the dendrite          | [18,19] |
| $m_{CaLLVA, dend, post}$      | $m_{\infty, CaLLVA, dend, post}$ | 1    | Gating variable for postsynaptic CaLLVA activation in the dendrite          | [18,19] |
| $m_{KA, dend, post}$          | $m_{\infty, KA, dend, post}$ | 1    | Gating variable for postsynaptic $K_A$ activation in the dendrite           | [18,19] |
| $m_{KDR, soma, post}$         | $m_{\infty, KDR, soma, post}$ | 1    | Gating variable for postsynaptic $K_{DR}$ activation in the soma            | [18,19] |
| $m_{Na, dend, post}$          | $m_{\infty, Na, dend, post}$ | 1    | Gating variable for postsynaptic $Na^+$ activation in the dendrite          | [18,19] |
| $m_{Na, soma, post}$          | $m_{\infty, Na, soma, post}$ | 1    | Gating variable for postsynaptic $Na^+$ activation in the soma             | [18,19] |
| $m_{NMDAR, post}$             | $m_{\infty, NMDAR, post}$ | 0    | Fraction of postsynaptic NMDARs in open state                               | [18,19] |

### Table W. Intermediate variables of astrocyte model.

| Intermediate variable | Description                                                                 | Refs |
|-----------------------|-----------------------------------------------------------------------------|------|
| $h_{\infty, astro}$   | $\frac{Q_{astro}}{Q_{astro} + [Ca^{2+}]_{astro}}$                         | [18,19] |
| $m_{\infty, astro}$   | $\frac{[IP_3]_{astro}}{K_{IP3,1, astro} + [IP_3]_{astro}}$                | [18,19] |
| $n_{\infty, astro}$   | $\frac{[Ca^{2+}]_{astro}}{K_{act, astro} + [Ca^{2+}]_{astro}}$            | [18,19] |
| $J_{IP3R, astro}$      | $v_{IP3R, astro}m_{\infty, astro}n_{\infty, astro}h_{\infty, astro} \{C_{tot, astro} - (1 + r_{ER cyt, astro})[Ca^{2+}]_{astro}\}$ | [18,19] |
| $J_{leakER, astro}$    | $r_{leakER, astro} \{C_{tot, astro} - (1 + r_{ER cyt, astro})[Ca^{2+}]_{astro}\}$ | [18,19] |
| $J_{SERCA, astro}$     | $v_{SERCA, astro} \frac{[Ca^{2+}]_{astro}^2}{K_{SERCA, astro}^2 + [Ca^{2+}]_{astro}^2}$ | [18,19] |
| $Q_{astro}$            | $K_{inh, astro} \frac{[IP_3]_{astro} + [IP_3]_{astro}}{K_{IP3,1, astro} + K_{IP3,2, astro}}$ | [18,19] |
| $\tau_{h, astro}$      | $\frac{1}{r_{IP3R, astro} \{Q_{astro} + [Ca^{2+}]_{astro}\}}$            | [18,19] |
| Parameter          | Value    | Unit     | Description                                                       | Refs   |
|--------------------|----------|----------|------------------------------------------------------------------|--------|
| $AG^{*}_{post}$    | 0.0010453| µM       | Postsynaptic resting 2-AG concentration                          |        |
| $C_{thr,astro}$    | 0.3      | µM       | $Ca^{2+}$ threshold concentration of Glu exocytosis in astrocytes| 59     |
| $Ca_{tot,astro}$   | 2        | µM       | Total free astrocytic $Ca^{2+}$ concentration                    | 18     |
| $G_{astro}$        | 50,000   | µM       | Glu concentration per astrocytic vesicle                         | 9      |
| $IP_{3,astro}$     | 0.28     | µM       | Astrocytic resting IP$_3$ concentration                          | 38, 0.16 µM |
| $k_{reco,astro}$   | 0.0006   | 1/ms     | Astrocytic recovery rate constant from empty to releasable state | 9      |
| $K_{act,astro}$    | 0.08234  | µM       | Astrocytic IP$_3$R dissociation constant of $Ca^{2+}$ (activation)| 18     |
| $K_{inh,astro}$    | 1.049    | µM       | Astrocytic IP$_3$R dissociation constant of $Ca^{2+}$ (inhibition)| 18     |
| $K_{IP3,1,astro}$  | 0.13     | µM       | Astrocytic IP$_3$R dissociation constant of IP$_3$              | 18     |
| $K_{IP3,2,astro}$  | 0.9434   | µM       | Astrocytic IP$_3$R dissociation constant of IP$_3$              | 18     |
| $K_{SERCA,astro}$  | 0.1      | µM       | Half-activation constant of astrocytic SERCA pump                | 18     |
| $N_{astro}$        | 4        | 1        | Number of readily releasable astrocytic vesicles                 | 9      |
| $P_{rel,astro}$    | 0.6      | 1        | Basal release probability of astrocytic Glu vesicles             | 9, 10  |
| $r_{astro}$        | 0.005    | 1/ms     | Glu clearance rate from extrasynaptic space                      | 10     |
| $r_{ERcyt,astro}$  | 0.185    | 1        | Ratio between astrocytic ER and cytosol volumes                  | 18     |
| $r_{IP3,astro}$    | 0.0008   | 1/ms     | Rate constant of astrocytic IP$_3$ production                    | 38     |
| $r_{IP3R,astro}$   | 0.0002   | µM/ms    | Astrocytic IP$_3$R binding constant for $Ca^{2+}$ (inhibition)  | 18     |
| $r_{leak,astro}$   | $\frac{J_{SERCA,astro} - J_{IP3R,astro}}{Ca_{tot,astro} - (1 + r_{ERcyt,astro}) [Ca^{2+}]_{astro}}$ | 1/ms | Astrocytic ER leak parameter calculated at resting concentrations | 18     |
| $r_{vesext,astro}$ | 0.00065  | 1        | Ratio between astrocytic vesicular volume and volume of extrasynaptic space | 9, 10  |
| $r_{IP3,astro}$    | 7,000    | ms       | Time constant for astrocytic IP$_3$ degradation                  | 38     |
| $r_{IP3R,astro}$   | 0.006    | 1/ms     | Maximum rate of $Ca^{2+}$ release via astrocytic IP$_3$R         | 18     |
| $v_{SERCA,astro}$  | 0.0007   | µM/ms    | Maximum rate of $Ca^{2+}$ uptake by astrocytic SERCA pump        | 18, 0.0009 µM/ms |
Table Y. Initial values of astrocytic variables.

| Variable         | Initial value | Unit | Description                                      |
|------------------|---------------|------|-------------------------------------------------|
| [Ca$^{2+}$]$_{astro}$ | 0.15002       | µM   | Astrocytic Ca$^{2+}$ concentration              |
| [Glu]$_{extsyn}$  | 0             | µM   | Concentration of Glu in extrasynaptic space     |
| $h_{astro}$       | $h_{\infty,astro}$ | 1    | Gating variable for astrocytic IP$_3$R inactivation |
| [IP$_3$]$_{astro}$ | 0.28          | µM   | Astrocytic IP$_3$ concentration                 |
| $R_{rel,astro}$   | 1             | 1    | Fraction of releasable astrocytic vesicles      |
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