Supplementary Material

Model Details

The core of the model is the astrocyte lane, as depicted in Fig. 1A of the paper. For the numerical solution, each astrocyte is represented by a rectangular cartesian grid with spacing 5μm, and thus contains 27 interior grid points and 98 surface grid points. The space between the cells is similarly represented by a rectangular grid of spacing 5μm that extends to ± 19 grid points in the y- and z-directions. At all points interior to the cells, diffusion and degradation of IP_3, and the release of Ca^{2+} from internal stores are implemented; at all surface points, the additional processes are ATP binding to receptors, the G-protein cascade leading to IP_3 production, and the release of ATP. The detailed equations for all these processes are given in (1). The extracellular points are used to implement the diffusion of ATP, with sinks at all boundaries.

As explained in the paper, it is not necessary to explicitly model the diffusion of glutamate in the extracellular space, so the neurons can be treated as points. The astrocytes release glutamate (Glu_A in Fig. 1B) as a result of the local action of ATP according to Eq. 1 of the paper; the [ATP] used in that equation is the average calculated over the complete surface of the astrocyte. This glutamate acts on NMDA receptors on the neurons according to §2.9 below; the term [Glu] in Eq. 39 is the concentration calculated using Eq. 1 in the paper. Glutamate is then released from the neurons (Glu_B in Fig. 1B) and acts on metabotropic glutamate receptors that are taken to be uniformly distributed over the astrocyte surface. In implementing the ion channel equations given below, the internal structure of the astrocytes is not used; rather, neurons, astrocytes and the extracellular space are treated as three compartments with volume ratios as specified in §2 below.

Fits to Glutamate Data

Eqs 1 and 2 of the paper come from least-squares fits to data, as shown in Figs. 1 and 2 below.

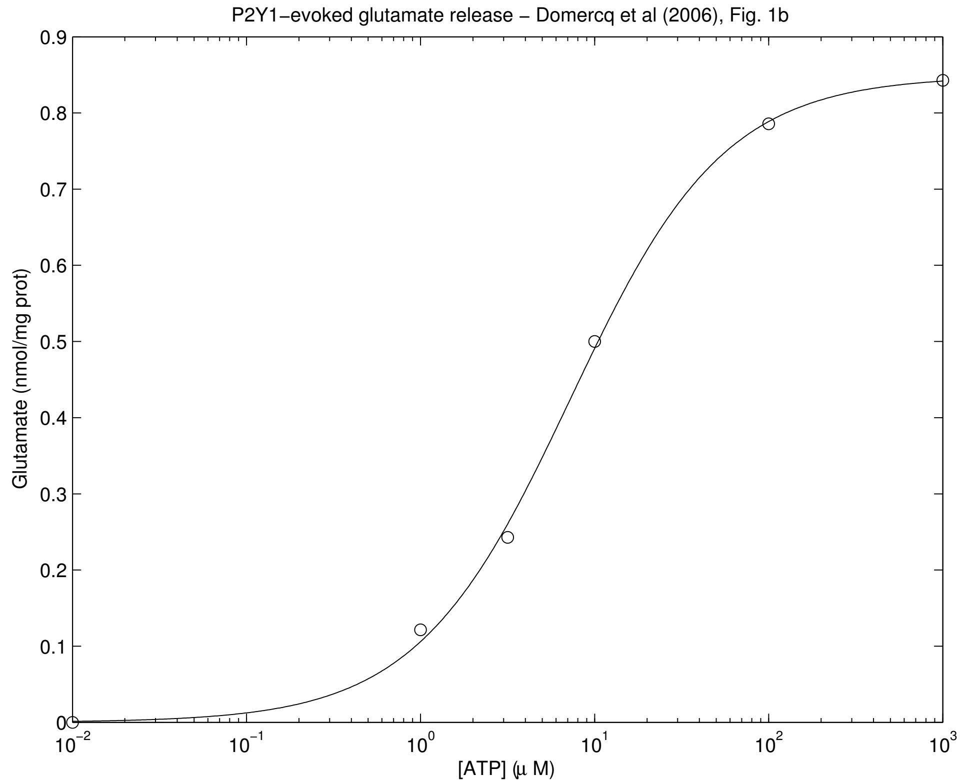

Figure 1: Least-squares fit to the data in Fig. 1b of (2). The circles give the data points and the line is the fit $0.85/(1 + 7.00[ATP]^{-0.98})$. $R^2 = 0.9990$.

Ion Channels

1 Basic equations

The total ionic current $I(t)$ through a specific ion channel type in a patch of membrane is given by Ohm's law:

$$I(t) = g(t, V)\,(V - E_S), \tag{1}$$

where V is the membrane potential, E_S is the reversal potential (Nernst potential) for the ionic species S under consideration and $g(t, V)$ is the total channel conductance for that membrane patch. In a Hodgkin-Huxley type

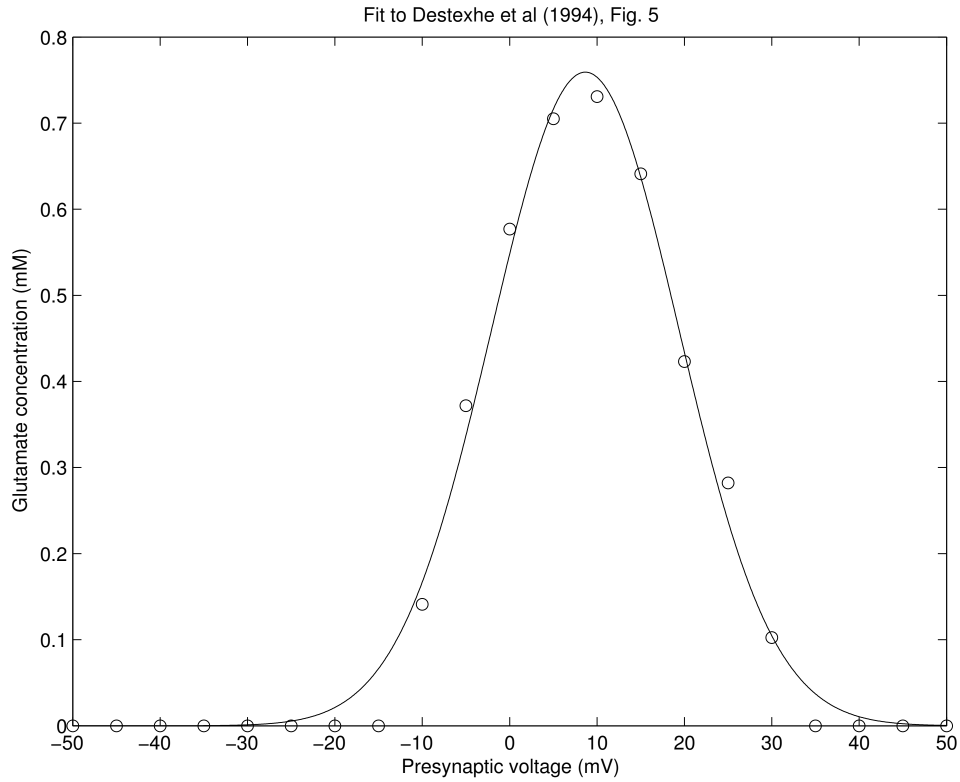

Figure 2: Least-squares fit to the open circles in Fig. 5 of (3). The circles give the data points and the line is the fit $0.76 \exp[-0.0044(V - 8.66)]$. $R^2 = 0.9918$.

formulation the conductance is given by

$$g(t, V) = \bar{g}\, m^i\, h^j, \tag{2}$$

where $\bar{g}$ is a constant, i and j are non-negative integers and $m \equiv m(t, V)$ and $h \equiv h(t, V)$ are activation and inactivation variables, respectively. For the case where the channel kinetics are fast compared with other times, as is the case in the present model, it is a good approximation to replace m and n in Eq. 2 by their equilibrium values; thus

$$g(t, V) \equiv g(V) = \bar{g}\, m_\infty^i\, h_\infty^j, \tag{3}$$

The Nernst potential is given by

$$E_S = \frac{RT}{zF} \ln \frac{[S]_0}{[S]_i}, \tag{4}$$

where $[S]_0$, $[S]_i$ are the ionic concentrations outside and inside the cell, respectively, and z is the charge on the ion. $R = 8.315$ J K^{-1} mol^{-1} is the gas constant, $F = 9.648 \times 10^4$ C mol^{-1} is Faraday's constant and T K is the absolute temperature. At 37 Celsius

$$E_S = \frac{26.73}{z} \ln \frac{[S]_0}{[S]_i}. \tag{5}$$

2 Specific channels

The following lists the equations for all the ion channels used in our model. In many cases, there is no unique formulation for a particular channel, and we have chosen the one that seems most appropriate in the present context. There are many inconsistencies in the literature on ion channels; here, we have attempted to give an accurate set of equations, correcting a number of misprints and unifying the notation. Units used are time (ms), area (μm^2), volume (μm^3), potential (mV), current density (pA μm^{-2}), conductance (nS μm^{-2}), concentration (mM), concentration change (mM s^{-1}). Following Dronne et al. (4), the neurons occupy 50% of the total space and the astrocytes occupy 30%. The volume to surface ratios are 5.56 and 3.58 for neurons and astrocytes, respectively.

2.1 Potassium delayed rectifier current, KDR (*neuron and astrocyte*)(4–6)

$$I_{KDR} = g_{KDR} m_\infty^2 h_\infty (V_m - E_K), \tag{6}$$

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}, \tag{7}$$

$$\alpha_m = \frac{0.0047(V_m - 8)}{1 - e^{-(V_m-8)/12}}, \tag{8}$$

$$\beta_m = e^{-(V_m+127)/30}, \tag{9}$$

$$h_\infty = \frac{1}{1 + e^{(V_m+25)/4}}. \tag{10}$$

2.2 Potassium BK current (***neuron and astrocyte***)(4–6)

$$I_{BK} = g_{BK} m_\infty (V_m - E_K), \tag{11}$$

$$m_\infty = \frac{250\,[\mathrm{Ca}^{2+}]_i\, e^{V_m/24}}{250\,[\mathrm{Ca}^{2+}]_i\, e^{V_m/24} + 0.1\, e^{-V_m/24}}. \tag{12}$$

2.3 Potassium M current (***neuron and astrocyte***)(5, 6)

$$I_{KM} = g_{KM}\, m_\infty\, (V_m - E_K), \tag{13}$$

$$m_\infty = \frac{1}{1 + e^{-(V+35)/10}}. \tag{14}$$

2.4 Potassium SK current (***neuron and astrocyte***)(5, 6)

$$I_{SK} = g_{SK}\, m_\infty^2\, (V_m - E_K), \tag{15}$$

$$m_\infty = \frac{1.25 \times 10^8\, [\mathrm{Ca}^{2+}]_i^2}{1.25 \times 10^8\, [\mathrm{Ca}^{2+}]_i^2 + 2.5}. \tag{16}$$

2.5 Potassium IK current (***neuron and astrocyte***)(7)

$$I_{IK} = \frac{g_{IK}\, m_\infty\, (V_m - E_K)}{(1 + 0.0002/[\mathrm{Ca}^{2+}]_i)^2}, \tag{17}$$

$$m_\infty = \frac{25}{0.075\, e^{-(V_m+5)/10} + 25}. \tag{18}$$

2.6 Fast Sodium current NaF (*neuron and astrocyte*)(7)

$$I_{NaF} = g_{NaF}\, m_\infty^3\, h_\infty\, (V_m - E_{Na}), \tag{19}$$

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}, \tag{20}$$

$$\alpha_m \quad = \quad 35\, e^{(V_m+5)/10}, \tag{21}$$

$$\beta_m \quad = \quad 7\, e^{-(V_m+65)/20}, \tag{22}$$

$$h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h}, \tag{23}$$

$$\alpha_h = \frac{0.225}{1 + e^{(V_m+80)/10}}, \tag{24}$$

$$\beta_h = 7.5\, e^{(V_m-3)/18}. \tag{25}$$

2.7 Persistent sodium current, NaP (*neuron and astrocyte*)(7)

$$I_{NaP} = g_{NaP}\, m_\infty^3\, (V_m - E_{Na}), \tag{26}$$

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}, \tag{27}$$

$$\alpha_m = \frac{200}{1 + e^{-(V_m-18)/16}}, \tag{28}$$

$$\beta_m = \frac{25}{1 + e^{(V_m+58)/8}}. \tag{29}$$

2.8 Calcium high voltage activated current (P-type) (***neuron and astrocyte***)(7)

$$I_{CaHVA} = g_{CaHVA}\, m_\infty\, h_\infty\, (V_m - E_{Ca}), \tag{30}$$

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}, \tag{31}$$

$$\alpha_m = \frac{8.5}{1 + e^{-(V_m - 8)/12.5}}, \tag{32}$$

$$\beta_m = \frac{35}{1 + e^{(V_m + 74)/14.5}}, \tag{33}$$

$$h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h}, \tag{34}$$

$$\alpha_h = \frac{0.0015}{1 + e^{(V_m + 29)/8}}, \tag{35}$$

$$\beta_h = \frac{0.0055}{1 + e^{-(V_m + 23)/8}}. \tag{36}$$

2.9 NMDA currents (***neuron***)(3, 8)

$$I_{NMDA} = g_{NMDA}\, G_{NMDA}(V_m)\, P_{open}(t)\, f(V_m), \tag{37}$$

$$G_{NMDA}(V) = \frac{1}{1 + 0.28\, e^{-0.062V}}, \tag{38}$$

$P_{open}(t) \equiv y(t)$ satisfies

$$\frac{dy}{dt} = r_1\, [\mathrm{Glu}]\, (1 - y) - r_2\, y, \tag{39}$$

where [Glu] (mM) is the glutamate concentration, $r_1 = 72$ $\mathrm{mM^{-1}\, s^{-1}}$ and $r_2 = 6.6\, \mathrm{s^{-1}}$.

$$f(V_m) = \phi_m \frac{[S]_i - [S]_o\, e^{-z\phi_m}}{1 - e^{-z\phi_m}}, \tag{40}$$

where $\phi_m = (F/RT)\, V_m$.

3 Pumps and exchangers

3.1 Chloride pump (*neuron and astrocyte*)(4)

$$I_{Clp} = -r_{Cl} \frac{[\mathrm{Cl}^-]_i}{[\mathrm{Cl}^-]_i + 25}. \tag{41}$$

3.2 Calcium pump (*neuron and astrocyte*)(4, 6)

$$I_{Cap} = r_{Ca} \frac{[\mathrm{Ca}^{2+}]_i}{[\mathrm{Ca}^{2+}]_i + .0002}. \tag{42}$$

3.3 Sodium/potassium pump (*neuron and astrocyte*)(4, 6)

$$I_{Kp} = -r_{NaK} \left(\frac{[\mathrm{K}^+]_o}{[\mathrm{K}^+]_o + 3.7} \right)^2 \left(\frac{[\mathrm{Na}^+]_i}{[\mathrm{Na}^+]_i + 0.6} \right)^3 f(\phi_m), \tag{43}$$

$$f(\phi) = \frac{0.052 \sinh \phi}{0.026\, e^{\phi} + 22.5\, e^{-\phi}}, \tag{44}$$

$$\phi_m = \frac{F}{RT}(V_m + 176.5), \tag{45}$$

$$I_{Nap} = -1.5\, I_{Kp}. \tag{46}$$

3.4 Sodium/calcium exchanger (*neuron and astrocyte*)(9)

$$I_{Caex} = -r_{NaCa} \frac{[\mathrm{Na}^+]_i^3\, [\mathrm{Ca}^{2+}]_o\, e^{0.35\phi_m} - 2.5[\mathrm{Na}^+]_o^3\, [\mathrm{Ca}^{2+}]_i\, e^{-0.65\phi_m}}{(87.5^3 + [\mathrm{Na}^+]_o^3)(1.38 + [\mathrm{Ca}^{2+}]_o)(1 + 0.1 e^{-0.65\phi_m})}, \tag{47}$$

$$\phi_m = (F/RT)\, V_m, \tag{48}$$

$$I_{Naex} = -1.5 I_{Caex}. \tag{49}$$

3.5 Potassium/chloride transporter (*neuron and astrocyte*)(4)

$$I_{Kex} = r_{KCl}\,\frac{RT}{F}\,\log\left(\frac{[\mathrm{K}^+]_i}{[\mathrm{K}^+]_o}\frac{[\mathrm{Cl}^-]_i}{[\mathrm{Cl}^-]_o}\right), \tag{50}$$

$$I_{Clex} = -I_{Kex}. \tag{51}$$

3.6 Sodium/potassium/chloride transporter (*astrocyte only*)(4)

$$I_{Ktr} = -r_{NaKCl}\,\frac{RT}{F}\,\log\left(\frac{[\mathrm{Na}^+]_o}{[\mathrm{Na}^+]_i}\frac{[\mathrm{K}^+]_o}{[\mathrm{K}^+]_i}\left(\frac{[\mathrm{Cl}^-]_o}{[\mathrm{Cl}^-]_i}\right)^2\right), \tag{52}$$

$$I_{Natr} = I_{Ktr}, \tag{53}$$

$$I_{Cltr} = -2I_{Ktr}. \tag{54}$$

4 Leaks

Basic equation:

$$I_{leak} = g_{leak}(V_m - E_S). \tag{55}$$

Leaks are present in both astrocytes and neurons for K^+, Na^+, Ca^{2+} and Cl^-. The corresponding parameters g_{leak} are set by balancing individual ionic fluxes to zero in the initial (equilibrium) state.

Extracellular Potential

The extracellular potential, V_{SD}, is calculated using (10):

$$\frac{dV_{SD}}{dx} = -\frac{RT}{F}\sum_i z_i\,D_i\frac{d[C_i]_{ext}}{dx}\Big/\sum_i z_i^2\,D_i\,[C_i]_{ext}, \tag{56}$$

where z_i is the valence and D_i is the diffusion coefficient for ionic species C_i and the sum is over the four ions Na^+, K^+, Cl^- and Ca^{2+}. Extracellular diffusion of ions is not explicitly included in our model, so it is necessary to interpolate between concentrations just outside a cell and concentrations at a distance, taken to be the equilibrium values. The simplest interpolation is a linear one:

$$[C_i]_{ext}(x) = \frac{c_i^A(x - x_B) - c_i^B(x - x_A)}{x_A - x_B}, \tag{57}$$

where c_i^A and c_i^B are the concentrations at x_A and x_B, respectively. Using this in Eq. 56 and integrating from x_A to x_B gives

$$V_B - V_A = -\frac{RT}{F} \frac{\sum_i z_i D_i(c_i^B - c_i^A)}{\sum_i z_i^2 D_i(c_i^B - c_i^A)} \log\left(\frac{\sum_i z_i^2 D_i c_i^B}{\sum_i z_i^2 D_i c_i^A}\right), \tag{58}$$

where V_A and V_B are the extracellular potentials at x_A and x_B, respectively. Taking c_i^A to be the equilibrium concentrations and c_i^B to be the concentrations as calculated in the vicinity of a cell, then allows us to find the potential.

A more realistic interpolation for the concentrations is the gaussian

$$[C_i]_{ext}(x) = c_i^A + (c_i^B - c_i^A)\, e^{-\beta(x_B - x)^2}, \tag{59}$$

where c_i^A is now the concentration as $x \to \infty$. Using this in Eq. 56 gives exactly the same answer as before (Eq. 58).

Symbol	Value Neuron	Value Astrocyte	Notes
g_{KDR}	2.0	35.0	(4)
g_{BK}	0.1	0.1	0.003-0.3 (5–7)
g_{KM}	0.01	0.01	0.0004-0.01 (5–7)
g_{SK}	0.005	0.005	0.001-0.0054 (5, 6)
g_{IK}	0.004	0.004	0.001-0.004 (6, 7)
g_{NaF}	60	60	(7)
g_{NaP}	0.002	0.002	0.0002-0.01 (4, 6, 7, 11)
g_{CaHVA}	0.02	0.02	0.018-0.02 (4, 6, 7)
g_{NMDA} (K^+)	0.0965		fitted
g_{NMDA} (Na^+)	0.0965		fitted
g_{NMDA} (Ca^{2+})	2.32		fitted
r_{Cl}	0.02	0.02	fitted
r_{Ca}	0.02	0.001	fitted
r_{NaK}	6.0	9.0	fitted
r_{NaCa}	10.0	10.0	fitted
r_{KCl}	0.00005	0.005	fitted
r_{NaKCl}		0.002	fitted

Table 1: Parameter values used for the ion channels. Some values are available in the literature, although in many cases there is a wide variation, indicated by the range of values indicated (for the neuron); others have been chosen to fit experimental data.

Ion	Neuron	Astrocyte	Extracellular
K^+	130	130	3.5
Na^+	10	10	140
Ca^{2+}	0.0001	0.0001	2
Cl^-	5	7	100

Table 2: Initial ionic concentrations (mM) (Cf. (4))

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