

A model of short term presynaptic plasticity as observed in neurons of the rodent striatum in response to fast glutamatergic inputs

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Abstract

A model to study short-term synaptic plasticity as observed in principal and local interneurons in the rodent striatum in response to glutamatergic synaptic input is presented.

1 Mathematical modeling of striatal neurons

The model dynamics are given by three ordinary differential equations that describe the time-dependent changes of v , w , and c , respectively representing the transmembrane potential, the proportion of open delayed rectifier K^+ channels, and the intracellular Ca^{2+} concentration (?).

The change in the membrane potential is the sum of the transmembrane ionic fluxes normalized by the membrane capacitance. Explicitly,

$$C_m \partial_t v = I_F - , \quad (1)$$

with

$$I_{In} = I_{NaT}(v, w) - I_{CaL}(v, c) - I_{DK}(v, w) - I_{SK}(v, c) - I_{NaK}(v) \quad (2)$$

$$I_{Syn} = -I_{GA}(v, u) - I_{AK}(v, c), \quad (3)$$

Here $\partial_t G$ represents the instantaneous change in G with respect to time. C_m (pF) is a constant representing the change in charge around the membrane with respect to the membrane potential typically referred to as membrane capacitance in conductance-based models, (?). The term I_F represents a stimulus *forcing* the membrane either by incoming current from an electrode, or from the local field potential (simulations of spontaneous activity). The fluxes in quation (1) are all given by the product of an amplitude term (pA), a gating term, a flux driving force (Table 1). The amplitude terms a_x are given by $s_x N_x$. The term s_x (pA) is the current flowing through a single transmembrane protein (typically around 1 pA for most voltage-gated channels (?)), and N_x is the number of membrane proteins mediating the current (e.g. number of K^+ channels). In our calculations and estimations of the contributions of the different ion fluxes to the change in v , we use $a_x = s_x N_x$ (pA) as an approximation for the whole-cell current. The flux across the membrane mediated by the different transmembrane transport mechanisms represented in the model is given by

$$F_x(v) = \exp\left(b_x g_x \frac{v - v_x}{v_T}\right) - \exp\left((b_x - 1) g_x \frac{v - v_x}{v_T}\right), \quad x \in \{N, C, K, NK\} \quad (4)$$

The term b_x in (4) represents the transport bias across the membrane in either direction for a given ion channel or pump ($b = 0.5$ means transmembrane transport is bidirectional and symmetrical, i.e. no rectification, which means assymetrical ion flux (?)). The thermal potential $v_T = kT/q$ (mV), where k is Boltzmann's constant (mJ/°K), T is absolute temperature (°K), and q is elementary charge (Coulombs). The Boltzmann constant can be thought of as a scaling factor between macroscopic (thermodynamic temperature) and microscopic (thermal energy) physics (?). The Nernst potential for each ion x (Na^+ , calcium, or K^+) is given by:

$$v_x = \frac{v_T}{z_x} \ln \left(\frac{[x]_o}{[x]_i} \right) \quad (5)$$

where z_x is the ion valence and $[x]_o$ and $[x]_i$ represent concentrations outside and inside the cell, respectively. The reversal potential for the Na-K ATPase is given by $v_{NaK} = 3v_{Na} - 2v_K - v_{ATP}$ (?).

Table 1: All ion fluxes are given by a product of the form $I_x = a_x G_x F_x$ where a_x , G_x , and F_x represent, respectively, the amplitude (normalized by membrane capacitance), gating, and driving force terms for the flux. The gating term for the Na^+ - K^+ pump can be written as 1, which can be thought of as saturation. Note that the inactivation of Na^+ -channels is also represented by w (?). The proportion of non-inactivated Na^+ channels is thus $1 - w$.

Mechanism	Name	Amplitude (a)	Gating (G)	Flux F
Transient Na current	$I_{NaT}(v, w)$	a_{Na}	$S_m(v)(1 - w)$	$F_{Na}(v)$
L-type Ca^{2+} current	$I_{CaL}(v, c)$	a_{Ca}	$S_n(v)$	$F_{Ca}(v)$
Delayed rectifier K^+ channel	$I_{DK}(v, w)$	a_{DK}	w	$F_K(v)$
SK Ca^{2+} -dependent K^+ channel	$I_{SK}(v, c)$	a_{SK}	$H_{SK}(c)$	$F_K(v)$
Na^+ - K^+ pump	$I_{NaK}(v)$	a_{NaK}	1	$F_{NaK}(v)$

Gating. The dynamics for w , the proportion of activated delayed-rectifier K^+ channels, are assumed to be logistic,

$$\partial_t w = r_w w (S_w(v) - w) R_w(v), \quad (6)$$

which yields better fits, and is more consistent with, the dynamics of activation in channel populations recorded in voltage-clamp experiments (???). The parameter r_w is the recovery rate for w toward its voltage-dependent steady state $S_w(v)$. The function R_w describes the voltage-dependence of the rate of activation of the channels.

The auxiliary functions for voltage-dependent gating are given by

$$S_j(v) = \frac{\exp \left(g_j \frac{v - v_j}{v_T} \right)}{1 + \exp \left(g_j \frac{v - v_j}{v_T} \right)}, \quad j \in \{m, n, w\} \quad (7)$$

$$R_j(v) = \exp \left(b_j g_j \frac{v - v_j}{v_T} \right) + \exp \left((b_j - 1) g_j \frac{v - v_j}{v_T} \right) \quad (8)$$

where g_j represents the steepness of the activation curve for $\text{Na}^+(m)$, $\text{Ca}^{2+}(n)$, or $\text{K}^+(w)$ channels; v_j represents the half-activation voltage for those channels, and b_j in (8) represents the asymmetry in the gating relative to voltage that biases the time constant for the gating process.

The gating of the SK channel is not voltage-dependent. Instead, it depends on intracellular Ca^{2+} -binding, its activation is modeled using a Hill equation that depends on the intracellular concentration of Ca^{2+} , as used to fit data from channel recordings (?):

$$G_{SK}(c) = \frac{c^2}{c^2 + c_{SK}^2} \quad (9)$$

where c_{SK} represents the half-activation Ca^{2+} concentration for the Ca^{2+} -dependent K^+ -channels.

For the dynamics of intracellular Ca^{2+} we assume recovery toward a steady state c_∞ at a rate r_c , with increments caused by the Ca^{2+} current J_{Ca} .

$$\partial_t c = r_c(c_\infty - c) - k_c J_{CaL}(v, c). \quad (10)$$

The term k_c in equation (10) is the conversion factor that accounts for the effect of Ca^{2+} flux across the membrane on the intracellular Ca^{2+} concentration.

Spontaneous activity is simulated by replacing the term J_F with a time-dependent, Ornstein-Uhlenbeck (OU) process with amplitude $a_F(t)$ (pA). The mean is represented by μ_F (pA) (drift term) (?) given by (??)

$$a_F(t + \delta) = a_F(t) \left(1 - \frac{\delta}{\tau_F} \right) + \left[\mu_F \delta + \eta(t) \sqrt{d_{Stim} \delta} \right], \quad (11)$$

where δ is a small time step, τ_F is a relaxation time, $\eta(t)$ is an independent white noise process with zero-mean and unit standard deviation. The process has a variance $\sigma_F^2 = d_F \delta / 2$ (pA), which means that d_F can be approximated if an estimation of the variance of the current a_F is available (??).

Change of variables to obtain numerical solutions. To simplify the numerics, we change variables

$$y = v/v_T,$$

and adjust all voltages accordingly as

$$y_l = v_l/v_T.$$

The new equation for the normalized voltage is

$$\partial_t y = \frac{\partial_t v}{v_T}$$

. To simplify the notation and reduce the number of operations during the numerical integration, we also reparametrize the amplitudes as

$$A_l = \frac{a_l}{v_T C_m}.$$

in units of 1/ms. The result is a new equation of the form

$$\partial_t y = J_F - A_{NaKa} F_{NaKa}(y) \quad (12)$$

$$- \left(A_{KaD} w + A_{KaSK} \frac{2}{c^2 + c_0^2} \right) F_K(y) \quad (13)$$

$$- A_{NaT} (1 - w) m_\infty(y) F_{Na}(y) - A_{CaL} m_{13\infty}(y) F_{Ca}(y, c), \quad (14)$$

with driving force terms of the form

$$F_l(y) = 2 \sinh \left(\frac{y - y_l}{2} \right),$$

for $l \in \{NaKa, KaD, KaSK, NaT, CaL\}$. The term J_F (1/ms) is the input current I_F (pA) divided by $v_T C_m$.

1.1 Parameters

The ionic currents were modeled to fit as closely as possible the biophysical properties of those carried by channel variants expressed in mammalian neurons, and specifically CA1 PCs, where data are available. For example, the DK current is based on that mediated by $K_v2.1$ channels, found to be the predominant channel underlying the delayed rectifier current in rat hippocampal neurons ?. The L-type Ca^{2+} current is based on that carried by $Ca_v1.2$ (class C) channels, found to be the predominant L-type channel isoform expressed in rat brain ?. Additional details about the model current parameters can be found in Table 2.

Wherever possible, model parameters were taken from studies in rodent (mice and rat) striatal neurons. If data were not available, we obtained parameters from other types of mammalian cell, or from studies of mammalian ion channels in expression systems like *Xenopus* oocyte. Physical constants and other parameters which we would not expect to vary, such as the intra- and extracellular concentrations of ions or the cellular capacitance, were fixed. Biophysical properties of the ion channels, such as their half-activation voltages, were also fixed. The parameters we varied were primarily those corresponding to maximum current amplitudes, which can change acutely due to modulation or channel phosphorylation (??), or chronically due to changes in ion channel expression that occur with age (???).

Table 2: Constants and parameters. Note $v_{NaK} = 3v_{Na} - 2v_K - v_{ATP}$.

parameter	description	value	units	reference
k	Boltzmann's constant	$1.381e^{-20}$	mJ/K	physical constant ?
q	elementary charge	$1.602e^{-19}$	C	physical constant ?
T	absolute temperature	$273.15 +$ 37	K	adjusted to mammalian body temperature of 37° ?

parameter	description	value	units	reference
C_m	membrane capacitance	25.0	pF	in range reported in rat CA1 PCs ?
a_{NaT}	amplitude of transient Na^+ current	1.5-3.5	pA	set to produce currents of ~ 3 -7 nA as recorded in CA1 PCs from rats (?) and guinea pigs ?
a_{CaL}	amplitude of L-type Ca^{2+} current	0.4 or 0.7	pA	set to produce currents of ~ 2 -3 nA or ~ 5 -6 nA as recorded in young and aged CA1 PCs, respectively (?)
a_{DK}	amplitude of delayed rectifier K^+ current	20-50	pA	set to produce currents of ~ 7 -10 nA as recorded from HEK cells expressing rat Kv2.1 and J_K in hippocampal neurons (?)
a_{SK}	amplitude of Ca^{2+} -dependent K^+ current	1.1-2.5	pA	set to produce currents of ~ 300 pA to 1.2 nA, depending on Ca^{2+} concentration, as recorded in SK-transfected cells ?
a_{NaK}	amplitude of Na^+/K^+ ATPase current	0.015-0.035	pA	set to produce currents of ~ 90 -250 pA, similar to but on high end of range recorded in hippocampal PCs ?
v_{Na}	Nernst potential for Na^+	65	mV	in range reported for mammalian cells ?
v_{Ca}	Nernst potential for Ca^{2+}	variable; baseline 135	mV	in range reported for mammalian cells ?
v_K	Nernst potential for K^+	-89	mV	in range reported for mammalian cells ?
v_{ATP}	Nernst potential for ATP	-450	mV	value used in model of mammalian heart cells and based on fit to data ?
v_{NaK}	Nernst potential for Na^+/K^+ ATPase	-76	mV	calculated based on the Nernst potentials for ATP, Na^+ , and K^+ , and a 3:2 stoichiometry, respectively (?)
r_w	rate of activation of delayed rectifier K^+ current	1.0-2.5	ms	in range recorded from CA1 PCs in slice (?) or hippocampal neurons in culture ?
s_m	symmetry of time constant of transient Na^+ current	0.5	-	based on voltage dependence of time constant recorded in rat CA1 PCs (?)
s_n	symmetry of time constant of L-type Ca^{2+} current	0.5	-	based on voltage dependence of time constant recorded in guinea pig CA1 PCs ?
s_w	symmetry of time constant of delayed rectifier K^+ current	0.3	-	based on fit; if higher (0.5-0.7) APs are the wrong shape and do not ride on sufficient plateau potential compared to recordings
v_m	half-activation potential of Na^+ current	-19	mV	in range reported for transient Na^+ channels in CA1 PCs (???)
v_w	half-activation potential of delayed rectifier K^+ current	-1	mV	in range reported for rat Kv2.1 channels expressed in COS-1 cells ?
v_n	half-activation potential of L-type Ca^{2+} current	3	mV	in range recorded for high-voltage activated Ca^{2+} currents in rat CA1 PCs ?; see also recordings from oocytes (?) or HEK cells (?) expressing $Ca_v 1.2$ channels
c_{SK}	half-activation Ca^{2+} concentration for SK current	740	nM	based on recordings from oocytes expressing rat SK channel variant (?)
z_m	activation slope of transient Na^+ current	4.0	-	
g_n	activation slope of L-type Ca^{2+} current	4.0	-	
g_w	activation slope of delayed rectifier K^+ current	4.0	-	fit to data from rat brain delayed rectifier channels ?
c_∞	minimum intracellular Ca^{2+} concentration	100	nM	approximate resting intracellular Ca^{2+} concentration reported in rat CA1 PCs (???)

parameter	description	value	units	reference
r_c	Ca ²⁺ removal rate constant	$8e^{-3}$ to $1e^{-3}$	-	adjusted to produce Ca ²⁺ dynamics as recorded in rat CA1 PCs (?)
k_c	Ca ²⁺ current to concentration conversion factor	$8e^{-6}$ to $6e^{-6}$	-	adjusted to produce Ca ²⁺ dynamics as recorded in rat CA1 PCs (?)

Table 3: Parameters used to produce different firing patterns in the yPC model. The normalization of amplitudes was calculated with $v_T C_m = 668.171$ mV pF. Amplitudes in pA are included (in parentheses) for reference with respect to experimental measures. The amplitude for the L-type Ca²⁺ current in the aPC was set to $a_{CaL}=467.719$ pA, which is equivalent to $A_{CaL}=0.7$ (1/ms)

parameter	adaptive firing	conditional bursting	spontaneous bursting
A_{NaK} (a_{NaK} pA)	0.015 (10.0226)	0.020 (13.3634)	0.040 (26.7268)
A_{KD} (a_{KD} pA)	40.0 (26726.8)	20.0 (13363.4)	30.0 (20045.1)
A_{SK} (a_{SK} pA)	1.1 (734.988)	2.5 (1670.43)	1.1 (734.988)
A_{Na} (a_{Na} pA)	1.5 (1002.26)	2.0 (1336.34)	4.0 (2672.68)
A_{CaL} (a_{CaL} pA)	0.4 (267.268)	0.4 (267.268)	0.4 (267.268)
r_{KD}	1.0	2.5	1.0
r_{Ca}	$1e^{-3}$	$5e^{-3}$	$1e^{-2}$
k_{Ca}	$8e^{-6}$	$6e^{-6}$	$6e^{-6}$