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A single compartment neuron model with activity-dependent conductances during NMDA induced activity

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Short communication

Abstract. In most neuron models the values of maximal conductances of membrane ionic currents are fixed. In our paper we investigate spiking activity of the neuron model activated tonically by NMDA synapse, when the membrane ionic currents are dynamically dependent on calcium concentration, as in a model by Abbott and coauthors (1993). A spiking neuron model (in Matlab/Simulink environment) is based on the properties of lamprey spinal neurons. The basic neuron is a one-compartment model with voltage-gated Na^+, K^+, Ca^{2+}, K_{Ca}^+ channels. The Na^+ and K^+ currents are described with the dynamic equations of Hodgkin-Huxley model (Hodgkin and Huxley 1952). The Ca^{2+} and K_{Ca}^+ channels are modeled using description of calcium dynamic introduced by Ekeberg and coauthors (1991). The model was tonically activated by NMDA synapse described by a kinetic model of synaptic transmission. We analyzed the activity of this model and showed that when only one of conductances is calcium-dependent, the cell is not able to react to and recover from external perturbations.

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The most of neuron models based on the conductance of membrane currents use fixed values of the conductances. However, it was shown that persistent depolarization of the cell is accompanied by slowly developing long-term reduction of neuronal calcium currents (Franklin et al. 1992), i.e., the intrinsic characteristics of a neuron can be modified by extracellular condition and neuron's activity. This phenomenon was analyzed by modeling studies, which investigated the possibility how the activity of a neuron may regulate its membrane currents (Abbott et al. 1993, LeMasson et al. 1993). These authors assumed that the intracellular calcium is a feedback element that plays a feedback role in regulating membrane currents. As the ionic membrane currents depend on the conductance of various ions (g_i), the steady state values of g_i should be intracellular calcium concentration [Ca] dependent, and given by equation (Abbott et al. 1993, LeMasson et al. 1993):

$$\tau \frac{dg_i}{dt} = f_i([Ca]) - g_i$$

where sigmoidal function $f_i([Ca])$ of the calcium concentration is defined by equation:

$$f_i([Ca]) = \frac{G_i}{1 + \exp[\pm([Ca] - C_T)/\Delta]}$$

where inward and outward currents are marked by the plus and minus sign, respectively. This choice has been made by the authors on the basis of stability arguments (LeMasson et al. 1993). The parameters determine a target calcium concentration (C_T) and the slope of the sigmoidal function (Δ). The maximal conductance g_i relaxes exponentially with a time constant τ, to an asymptotic value determined by $f_i([Ca])$.

In this way the electrical activity of the cell associated with the calcium inward currents will influence the calcium concentration inside the cell. The maximal conductances depend on the Ca^{2+} ions concentration what provides them ability to shift their values according to the changes induced by any factor. The time constant τ controls the speed of approach to the equilibrium. Although the process of approaching the equilibrium lasts much longer (Franklin et al. 1992), we set τ values to 50 s to speed up the simulation processes. It does not influence the general conclusions.

This sigmoidal function was applied to our realistic model of spiking neuron, constructed in Matlab/Simulink environment. It is a relatively simple model cell with one compartment and includes conductance-based models of ionic currents and synaptic conductances.

Mechanism of the membrane potential generation is based on the basic Hodgkin-Huxley model (Hodgkin and Huxley 1952), incorporating various membrane conductances. The dynamical equation for the membrane voltage is:

$$C_m \frac{dV}{dt} = -I_{Na} - I_K - I_{Ca} - I_{K(Ca)} - I_L \qquad (\rightarrow A1)$$

where C_m is capacitance of the membrane, and V is the membrane potential. (Note that in the parentheses we refer to the equations in the Appendix, where all values of parameters are provided.) Ionic currents of a given type of channel are described by equations provided below, and the leakage current is calculated as:

$$I_L(V) = g_L(V - V_L) \qquad (\rightarrow A2)$$

This is a nonspecific, passive cation current through the membrane, modeled with a conductance g_L across the membrane, with the equilibrium potential set close to the resting potential of the simulated cell.

The Na^+ current in the neuron model is limited to the largest component. The fast, transient I_{Na} is calculated according to the equation:

$$I_{Na}(V, m, h) = g_{Na} m^3 h (V - V_{Na}) \qquad (\rightarrow A3)$$

where g_{Na} is the maximal Na^+ channel conductance, V_{Na} is the reversal potential of Na^+ channel, the gating variables m and h are expressed in terms of rate constants (α_m and β_m) (Hodgkin and Huxley 1952) and determined by equations:

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \qquad (\rightarrow A4)$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \qquad (\rightarrow A5)$$

Incorporation of the sigmoidal function was done by changing the equations describing every membrane current by general function:

$$I_i(V,a,b,[Ca]) = g_i([Ca])a^x b^y (V - V_i)$$

The K^+ channel is treated in a similar way, except that inactivation is not included. A delayed-rectified K^+ current is given by:

$$I_K(V,n) = g_K n^4 (V - V_K) \qquad (\rightarrow A6)$$

where V_K is the reversal potential of the K^+ channel, g_K is the maximal conductance of the channel, and the gating variable n (as the degree of activation of the K^+ channels) is determined by equation:

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n \qquad (\rightarrow A7)$$

These equations describe a model capable of producing action potentials with a realistic shape. By adding the calcium dependent potassium channels the neuron model may repetitively fire spikes in a physiological frequency range. The implementation of the calcium dependent potassium current is based on the equations proposed by Ekeberg and coauthors (1991).

The depolarization during the action potential activates high-voltage activated (HVA) calcium channels, causing an inward depolarizing flow of Ca^{2+} ions. These channels are activated at a higher degree of depolarization than sodium and potassium channels (Tsien et al. 1988), open rapidly but close slowly, thus most of the Ca^{2+} enters after the action potential. The HVA calcium current is described by:

$$I_{Ca}(V,q) = g_{Ca} q^5 (V - V_{Ca}) \qquad (\rightarrow A8)$$

where V_{Ca} is the reversal potential of the Ca^{2+}, g_{Ca} is the maximal conductance of this channel, and q denotes the degree of activation of the calcium channels:

$$\frac{dq}{dt} = \alpha_q(1-q) - \beta_q q \qquad (\rightarrow A9)$$

The amount of the calcium within the cell depends both on the influx caused by the action potential, and the decay due to diffusion, buffering and other mechanisms. The intracellular calcium level $[Ca_{AP}]$ related to the spiking activity is given by the equation:

$$\frac{d[Ca_{AP}]}{dt} = q^5 \rho_{AP}(V - V_{Ca}) - \delta[Ca_{AP}] \qquad (\rightarrow A11)$$

where ρ_{AP} is the coefficient describing the rate of influx of Ca^{2+} ions and δ_{AP} is the coefficient describing the rate of decay of Ca^{2+} ions level.

The calcium dependent potassium current is described by:

$$I_{K(Ca)}(V,[Ca_{AP}]) = g_{K(Ca)}[Ca_{AP}](V - V_{K(Ca)}) \qquad (\rightarrow A10)$$

where $V_{K(Ca)}$ is the reversal potential of the $K(Ca)$ channel, and $g_{K(Ca)}$ is the maximal conductance of the channel.

Another calcium permeable channel is the N-methyl-D-aspartate (NMDA) glutamate receptor. Activation of this channel causes the influx of Ca^{2+} into the cell and increases the intracellular calcium concentration.

We modeled the synaptic NMDA input using the synaptic conductance, described by a first-order kinetic model of neurotransmitter binding to postsynaptic receptors. The model and kinetic parameters were borrowed from Destexhe and Pare (1999). In general, a synaptic current can be expressed (Destexhe et al. 1995, 1998) as a product of maximal synaptic conductance (g_{syn}), probability that a given channel is open (s) and synaptic equilibrium potential (V_{syn}):

$$I_{syn} = g_{syn} s\,(V - V_{syn})$$

The relation between the presynaptic potential and concentration of neurotransmitter in the synaptic cleft can be described by equation:

$$[T](V_{pre}) = \frac{T_{\max}}{1 + \exp\left[-\frac{(V_{pre} - V_p)}{K_p}\right]} \qquad (\rightarrow A12)$$

where T_{max} is the maximal concentration of neurotransmitter, V_{pre} the presynaptic potential. The parameters providing the steepness (K_p) and the value at which the function is half-activated (V_p), were set to the values used by Destexhe and coauthors (1998).

The NMDA type of glumate receptors can be described by a two-state model similar to AMPA, with

a voltage-dependent term representing magnesium block. The NMDA current is given by:

$$I_{NMDA} = g_{NMDA} B(V) r (V - V_{NMDA}) \qquad (\rightarrow A13)$$

where g_{NMDA} is the maximal conductance, V is the post-synaptic potential, V_{NMDA} is the reversal potential, $B(V)$ is the magnesium block and r describes the probability that the channel is open. The magnesium block of the NMDA receptor channel is given by an instantaneous function of voltage (Jahr and Stevens 1990):

$$B(V) = \frac{1}{1 + \exp(-0.062V)[Mg^{+2}]_0 / 3.57} \qquad (\rightarrow A14)$$

where $[Mg^{2+}]$ is the external magnesium concentration.

The r parameter is given by:

$$\frac{dr}{dt} = \alpha_{NMDA}[T](1 - r) - \beta_{NMDA}\, r \qquad (\rightarrow A15)$$

The amount of calcium ions entering through open NMDA channel $[Ca_{NMDA}]$ (Mayer et al. 1987) can be described by equation used by Ekeberg and coauthors (1991):

$$\frac{d[Ca_{NMDA}]}{dt} = r\rho_{NMDA}(V - V_{Ca(NMDA)}) - \delta_{NMDA}[Ca_{NMDA}] \qquad (\rightarrow A16)$$

where ρ_{NMDA} is the coefficient describing the rate of influx of Ca^{2+} ions and δ_{NMDA} is the coefficient describing the rate of decay of Ca^{2+} ions level entering the cell trough open NMDA channel, $V_{Ca(NMDA)}$ is the equilibrium potential for the NMDA synapse.

Finally, the Ca^{2+} ions concentration is given by equation:

$$[Ca] = [Ca_{AP}] + [Ca_{NMDA}]$$

Analyses of the impact of various values of conductances on the neuron model activity were done both for the fixed values (classical model) and with the sigmoidal function describing the relation between the conduction and the level of Ca^{2+} ions.

In all simulations the neuron model was under tonic stimulation of NMDA synapse. Setting the calcium conductance to various values induces different types of the cell activity, as shown in Fig. 1. High and low g_{Ca} values induce tonic activity with high or low frequency of action potentials. For the range between these values the cell shows a bursting activity, frequency of which is increasing with the lowering of the g_{Ca} value. This shows how much the level of Ca^{2+} ions influences the type of response of the cell. The neuron model with fixed values of conductances is not able to adjust to disturbances induced, e.g., by changes in the cell environment. In response to an increase of equilibrium potential V_K to -60 mV (what is equal to increasing the extracellular concentration of K^+ in experiments done by Franklin and coauthors (1992)), the cell is turning from NMDA induced oscillations to a long lasting tonic, high frequency activity.

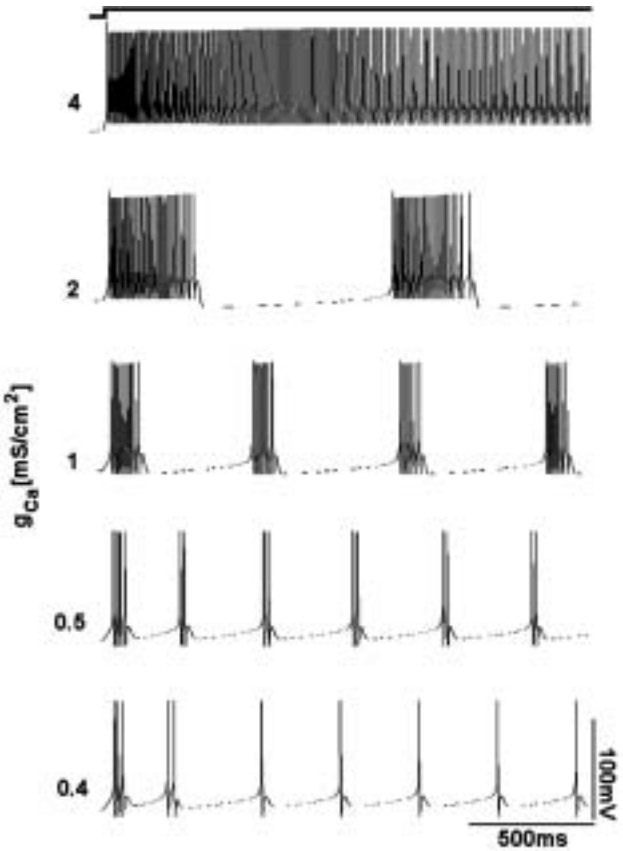

Fig. 1. Activity of the neuron model stimulated by tonic excitation of NMDA synapse (the top row) at different values of calcium conductance (g_{Ca} shown on the left side). At the highest g_{Ca} cell tonically fires a train of spikes. Decreasing of the g_{Ca} turns the cell into a bursting mode with increasing frequency of oscillations. Decrease of g_{Ca} has stronger impact on the burst duration than on the period between the burst.

It was shown, that dynamically regulated conductances may provide a neuron with a tool enabling preservation of the original pattern of activity (Abbott and LeMasson 1993, LeMasson et al. 1993). Our analysis was aimed at answering the question whether such preservation is possible in a neuron driven by tonic excitation of NMDA synapse, and whether it is enough to apply the sigmoidal function to only one of conductance currents at a time.

The response of the cell with all ion currents dependent on the Ca^{2+} level to the external perturbation (V_K = -60 mV) was similar in the pattern (shown in Fig. 2) to the effects observed by others (Abbott and LeMasson 1993, LeMasson et al. 1993). This proved that application of specific drive by NMDA synapse is as effective as the depolarization procedure used by LeMasson and coauthors (Abbott and LeMasson 1993, LeMasson et al. 1993). The cell was exhibiting bursting activity induced by NMDA stimulation until the moment, when the V_K was set to -60 mV. From this moment the cell started tonic spiking for about one second, and after that period it returned to the bursting pattern present before the perturbation.

Having proved that tonic NMDA stimulation of the cell may allow it to self-assemble the conductances and preserve the pattern of activity, we investigated behavior of the neuron models with single g_i

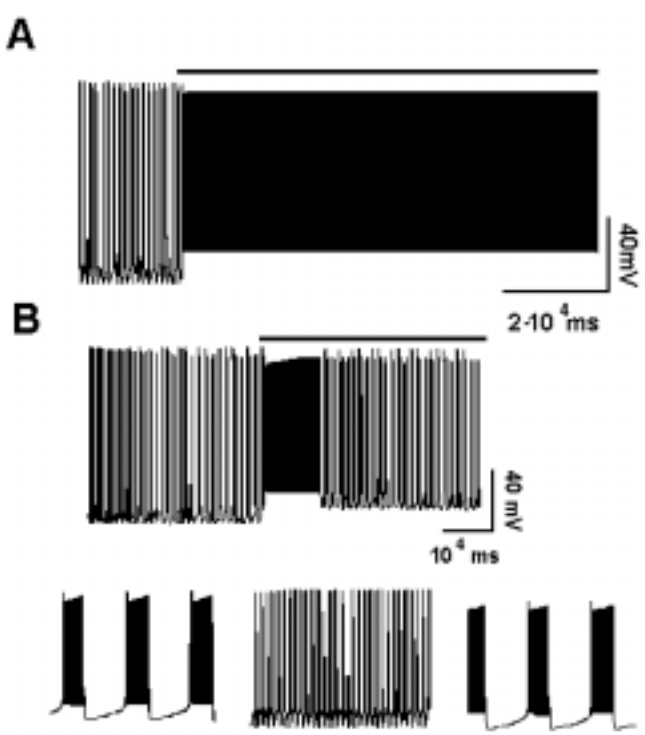

Fig. 2. (A) Response of the neuron model with fixed values of conductances to the external perturbation (V_K = -60 mV) marked by a line above the activity record, when tonically driven by NMDA synapse. The cell switches to tonic activity mode and do not readjust. (B) The response of the same neuron, but with all ion currents dependent on the Ca^{2+} level, to the same external perturbation. The cell is exhibiting bursting activity induced by NMDA stimulation until the moment, when the V_K was set to -60 mV. From this moment the cell starts tonic spiking for a second, and after that period it returns to the bursting pattern present before the perturbation. Examples of these patterns are shown at the bottom.

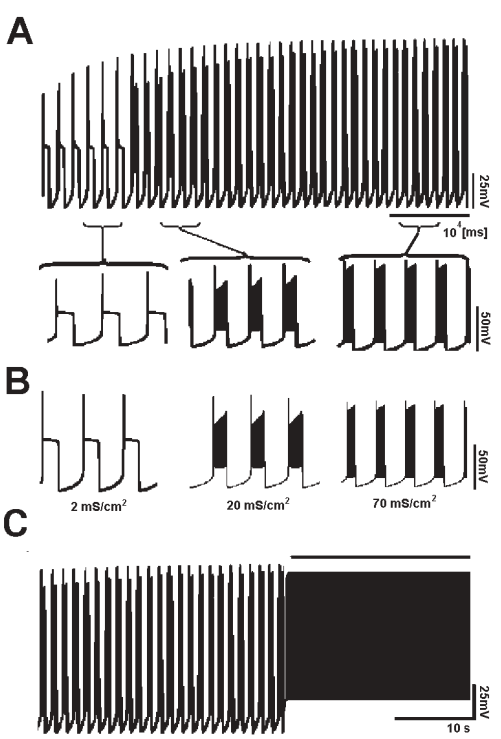

Fig. 3. (A) Behavior of the cell with g_{Na} conductance described by a sigmoidal function of calcium concentration. The cell is driven by tonically active NMDA synapse. At the beginning the cell starts with NMDA induced oscillations. The frequency of bursts decreases, when the g_{Na} increases to a threshold value for generating spikes. (B) The NMDA induced activity in a neuron with fixed values of g_{Na} (shown at the bottom) corresponding to the activity shown above. (C) Behavior of the cell with g_{Na} conductance modified according to sigmoidal function, when the external perturbation (V_K = -60 mV) was introduced (the horizontal line above the activity record).

conductance being influenced by Ca^{2+} ions. In Fig. 3A we show the behavior of the cell with g_{Na} changing in a time when the cell is excited by NMDA synapse. At the very beginning of the simulation the cell starts with NMDA induced oscillations, but it does not fire action potentials (the situation resembling application of TTX). Increase of g_{Na} leads to a decrease of burst duration. Setting the value of V_K to -60 mV resulted in switching by the cell to tonic activity without any readjustment to the previous bursting activity (Fig. 3C).

Similar effects were visible when the calcium dependent potassium current was set to be a sigmoidal function of Ca^{2+} ions concentration. At the beginning the cell produces NMDA induced burst (the upper raw in Fig. 4), but after this burst the activity becomes tonic with the decreasing frequency (see bottom row).

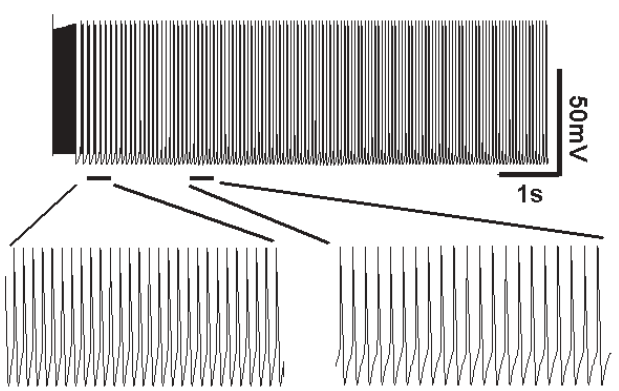

Fig. 4. Behavior of the cell with $g_{K(Ca)}$ conductance described by a sigmoidal function of calcium concentration. The cell is driven by tonically active NMDA synapse. At the beginning the cell starts with NMDA induced oscillations (low values of $g_{K(Ca)}$), but is able to generate only one burst of such activity. For higher values of $g_{K(Ca)}$ the cell shows a tonic pattern of activity (examples shown at the bottom with extended time scale).

Concluding, the results of our simulations show that the sigmoidal function is effective in a realistic model with burst activity induced by tonic NMDA synaptic excitation. The cell can readjust its activity and shift g_i values in such a manner that the general pattern of activity is preserved, like in a neuron model exposed to the increased amount of extracellular potassium (Abbott and LeMasson 1993, LeMasson et al. 1993). Our simulations show that providing only one conductance with such feature (a sigmoidal function of calcium concentration) does not allow the cell to adjust to external perturbations, what is possible in a model with all calcium-dependent membrane conductances.

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APPENDIX

The values of parameters used for simulations of the neuron model are presented with the equations.

Membrane potential:

$$C_m \frac{dV}{dt} = -\sum_i I_i \qquad \text{(A1)}$$

$C_m = 1$ μF cm^{-2}

Leak current I_L:

$$I_L(V) = g_L(V - V_L) \qquad \text{(A2)}$$

$g_L = 0.83$ mS cm^{-2} , $V_L = -70$ mV

Sodium current I_{Na}:

$$I_{Na}(V, m, h) = g_{Na} m^3 h (V - V_{Na}) \qquad \text{(A3)}$$

$g_{Na} = 167$ mS cm^{-2} , $V_{Na} = 50$ mV

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m \quad , \qquad \text{(A4)}$$

$$\alpha_m = \frac{0.2(V+40)}{1-\exp(-40-V)} \quad , \quad \beta_m = \frac{0.06(-49-V)}{1-\exp\left[\frac{V+49}{20}\right]}$$

$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h \quad , \qquad \text{(A5)}$$

$$\alpha_h = \frac{0.08(-40-V)}{1-\exp(V+40)}, \quad \beta_h = \frac{1}{1+\exp\left[\frac{-36-V}{2}\right]}$$

Potassium current I_K:

$$I_K(V,n) = g_K n^4 (V - V_K) \tag{A6}$$

g_k = 83 mS cm^{-2}, V_k = – 80 mV;

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n, \tag{A7}$$

$$\alpha_n = \frac{0.02(V+31)}{1-\exp(-31-V)}, \quad \beta_n = \frac{0.005(-28-V)}{1-\exp\left[\frac{V+28}{0.4}\right]}$$

Calcium current I_{Ca}:

$$I_{Ca}(V,q) = g_{Ca} q^5 (V - V_{Ca}) \tag{A8}$$

g_{Ca} = 0.6 mS cm^{-2}, V_{Ca}= 150 mV

$$\frac{dq}{dt} = \alpha_q(1-q) - \beta_q q, \tag{A9}$$

$$\alpha_q = \frac{-0.08(V-10)}{1-\exp\left[\frac{(-10-V)}{11}\right]}, \quad \beta_q = \frac{0.001(-10-V)}{1-\exp\left[\frac{V+10}{0.5}\right]}$$

Calcium dependent potassium current $I_{K(Ca)}$:

$$I_{K(Ca)}(V,C) = g_{K(Ca)}[C](V - V_K) \tag{A10}$$

$g_{K(Ca)}$ = 0.6 mS cm^{-2}

$$\frac{d[Ca_{AP}]}{dt} = q^5 \rho_{AP}(V - V_{Ca}) - \delta_{AP}[Ca_{AP}] \tag{A11}$$

ρ_{AP} = 4 mV^{-1} s^{-1}, δ_{AP} = 20 s^{-1}

Synaptic currents:

$$C + nT \leftrightarrow O$$

$$[T](V_{pre}) = \frac{T_{\max}}{1+\exp\left[-\frac{(V_{pre}-V_p)}{K_p}\right]} \tag{A12}$$

T_{max} = 1 mM, K_p = 5 mV, V_p = 2 mV

NMDA current I_{NMDA}:

$$I_{NMDA} = g_{NMDA} B(V) r (V - V_{NMDA}) \tag{A13}$$

$g_{NMDA} = 2\ \text{mS cm}^{-2}$, $V_{NMDA} = 0\ \text{mV}$

$$B(V) = \frac{1}{1+\exp(-0.062V)[Mg^{+2}]_0 / 3.57} \tag{A14}$$

$[Mg^{2+}]_0 = 1 - 2\ \text{mM}$

$$\frac{dr}{dt} = \alpha_{NMDA}[T](1-r) - \beta_{NMDA}\, r \tag{A15}$$

α_{NMDA}= 7.2 × 10^{-2} ms^{-1}, β_{NMDA}= 6.6 × 10^{-3} s^{-1}

[Ca_{NMDA}] pool:

$$\frac{d[Ca_{NMDA}]}{dt} = r\rho_{NMDA}(V - V_{Ca(NMDA)}) - \delta_{NMDA}[Ca_{NMDA}] \tag{A16}$$

ρ_{NMDA} = 0.4 mV^{-1} s^{-1}, δ_{NMDA} = 2 s^{-1}, $V_{Ca(NMDA)}$= 20 mV

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