Macroscopic model of postsynaptic current activation considering presynaptic short term synaptic plasticity and postsynaptic activation

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Abstract

Postsynaptic currents depend on the activation of postsynaptic receptors, which depend on presynaptic release of neurotransmitter. In turn, the total postsynaptic current in response to the activation of synapses from a given presynaptic contact depends on the number of synapses in the contact and the probability of activation of the synapses in the contact.

1 Short term presynaptic plasticity model

Assume that the intracellular calcium concentration at the presynaptic terminal follows linear decay dynamics toward a steady state according to

$$\partial_t c = \frac{c_\infty - c}{\tau_c} + k_c \sum_{i=1}^{N} \delta(t_i). \tag{1}$$

where k_c (μM / pC) can be thought of as a rate indicating the impact of the net transmembrane flux of calcium on the intracellular concentration of calcium. As a rule of thumb, the value of k_c should be such that the change in the calcium concentration in a presynaptic terminal after a single action potential could be between 50 and 100 μM.

Consider synapses in which the probability of activation of the release machinery depends directly upon binding of calcium, and when unbound, decreases linearly. The dynamics for p can then be

$$\partial_t r = \alpha c^n (1 - r) - \beta r \tag{2}$$

$$\partial_t q = q \left(\frac{q_\infty - q}{\tau_q} \right) - rq \tag{3}$$

with α in ms$^{-1} \cdot \mu$M^{-n} and β in ms^{-1}.

Where c, r, q represent the calcium intracellular concentration, an activation variable of neurotransmitter release and the normalized proportion of neurotransmitter ready to be releasable respectively. Equation (2) can be rewritten as

$$\partial_t r = \frac{r_\infty(c) - r}{\tau_r(c)} \tag{4}$$

with

$$\tau_r(c) = \frac{1}{\alpha c^n + \beta} = \frac{1}{\alpha} \left(\frac{1}{c^n + \frac{\beta}{\alpha}} \right) \tag{5}$$

$$r_\infty(c) = \frac{c^n}{c^n + \frac{\beta}{\alpha}} \tag{6}$$

The fraction β/α is the calcium concentration at which the steady state for p. So let $c_m^n = \beta/\alpha$.

If the recovery of p is fast enough, let $p \approx p_\infty(c)$, them the system can be reduced to a 2-d system where dynamic of p is $p_\infty(c)$. The system (1)-(2)

$$\partial_t c = \frac{c_\infty - c}{\tau_c} - k_c I_{Ca} \tag{7}$$

$$\partial_t x = x \frac{x_\infty - x}{\tau_x} - p_\infty(c) x \tag{8}$$

$\partial_t c = \frac{c_\infty - c}{\tau_c} - k_c I_{Ca}$

Parameter	Value	Units	Description
c_∞	0.050	μM	Steady state concentration for intracellular calcium (**?**)
x_∞	1.0	μM	Steady state for the readily releasable pool
β/α	~ 0.001	ms	(**?**)
$c_m = (\beta/\alpha)^{1/n}$	50	μM	Half activating calcium concentration
k_c	0.1		Impact of the voltage-dependent calcium current on the intracellular calcium so that peaks are about 50 μM (**?**)
τ_c	30.0	ms	recovery time constant of intracellular calcium concentration
τ_x	20.0	ms	Recovery time constant for the readily releasable pool
n	4		()

1.1 Analysis considering delta pulses to predict asymptotic behaviours

$$\partial_t c = \frac{c_\infty - c}{\tau_c} - k\sum_{i=1}^{n}\delta(t-t_i) \tag{9}$$

$$\partial_t x = x\frac{x_\infty - x}{\tau_x} - p_\infty(c)x \tag{10}$$

$$\partial_t p = \frac{p_\infty(c) - p}{\tau_p} \tag{11}$$

$$p_\infty(c) = \frac{c^k}{c^k + \frac{\beta}{\alpha}} \tag{12}$$

Calcium dynamics: $c_\infty = 0, c_0 = c(t_0) = k$
Pulse times: $t_0, t_1, ..., t_n$

$$\begin{aligned}
c_0 &= c(t_0) = k \\
c(t) &= c_0 e^{-(t-t_0)/\tau_c} = k e^{-(t-t_0)/\tau_c}, \quad t_0 \le t < t_1 \\
c_1 &= c(t_1) = k\left(1 + e^{-(t_1-t_0)/\tau_c}\right) \\
c(t) &= c_1 e^{-(t-t_1)/\tau_c}, \quad t_1 \le t < t_2 \\
c_2 &= k + c_1 e^{-(t_2-t_1)/\tau_c} \\
&= k + k\left(1 + e^{-(t_1-t_0)/\tau_c}\right) e^{-(t_2-t_1)/\tau_c} \\
&= k + k\left(e^{-(t_2-t_1)/\tau_c} + e^{-(t_2-t_0)/\tau_c}\right) \\
&= k\left(1 + e^{-(t_2-t_1)/\tau_c} + e^{-(t_2-t_0)/\tau_c}\right)
\end{aligned}$$

Therefore, after the nth pulse has arrived,

$$c_n = k\left(\sum_{i=0}^{n} e^{-(t_n-t_i)/\tau_c}\right) \tag{13}$$

$$c(t) = c_n e^{-(t-t_n)/\tau_c}, \quad t_n \le t < t_{n+1} \tag{14}$$

If pulses are periodic (fixed frequency), with $\delta = t_{i+1} - t_i$, then $t_n - t_0 = n\delta$, and equation (13) transforms into

$$c_n = k\left(\sum_{i=0}^{n} e^{-i\delta/\tau_c}\right) \tag{15}$$

The quantity $a = e^{-\delta/\tau_c}$ represents the decay factor between pulses for calcium. Then the calcium concentration peak after the nth pulse is

$$c_n = k\left(\sum_{i=0}^{n} a^i\right) = k\left(\frac{1-a^{n+1}}{1-a}\right) \tag{16}$$

For instance, if $\delta = 50$ ms and $\tau_c = 10$ ms, then $a = e^{-5}$, which means that there is almost no accumulation of intracellular calcium between pulses at 20 Hz.

2 Qualitative Analysis of the Autonomous System

Model (9)-(12) is a kind of non autonomus differential equation with a finite number of time-dependent moments (delta pulses). Between each delta pulse, the model can be interpreted as a continuous autonomus system which is topologically equivalent to each other defined on different between pulses interval. Each of these autonomus systems has the form:

$$\partial_t c = \frac{c_\infty - c}{\tau_c} \tag{17}$$

$$\partial_t x = x\frac{x_\infty - x}{\tau_x} - p_\infty(c)x \tag{18}$$

whose nullclines are easily calculated:

$$c = c_\infty \tag{19}$$

$$x = x_\infty - \tau_x p_\infty(c) \qquad and \tag{20}$$

$$x = 0 \tag{21}$$

and whose equilibrium points also are easily calculated to be $(0,0)$ and $(0, x_\infty)$. The Jacobian matrix can be expressed as

$$J[f] = \begin{pmatrix} -\frac{1}{\tau_c} & 0 \\ p'(c_a)hx & \frac{x_\infty - 2x}{\tau_x} - hp_\infty(c_a) \end{pmatrix} \tag{22}$$

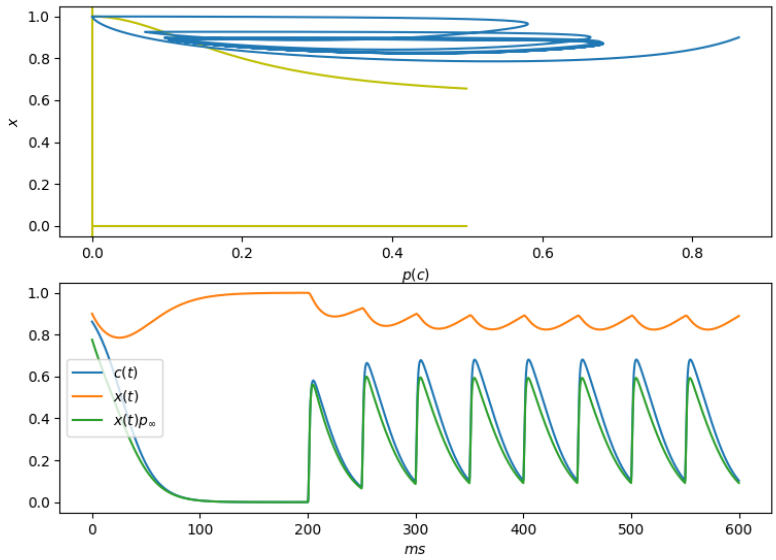

Figure 1: phase portrait and temporal courses of a facilitation configuration

so that is possible to known the stability at each point if equilibrium which just depend on the values of parameters τ_c and τ_x. Evaluating the Jacobian matrix at the fixed point $(0,0)$ we obtain

$$J_{(0,0)}[f] = \begin{pmatrix} -\frac{1}{\tau_c} & 0 \\ 0 & \frac{x_\infty}{\tau_x} \end{pmatrix} \tag{23}$$

so the fixed point is a saddle. While at the point $(0, x_\infty)$ Jacobian matrix is:

$$J_{(0,0)}[f] = \begin{pmatrix} -\frac{1}{\tau_c} & 0 \\ 0 & -\frac{x_\infty}{\tau_x} \end{pmatrix} \tag{24}$$

So in this case the fixed point is ever a stable node. As we can see, there is not bifurcations depending on parameters τ_x or τ_c at each autonomous model obtained of (9)-(12).

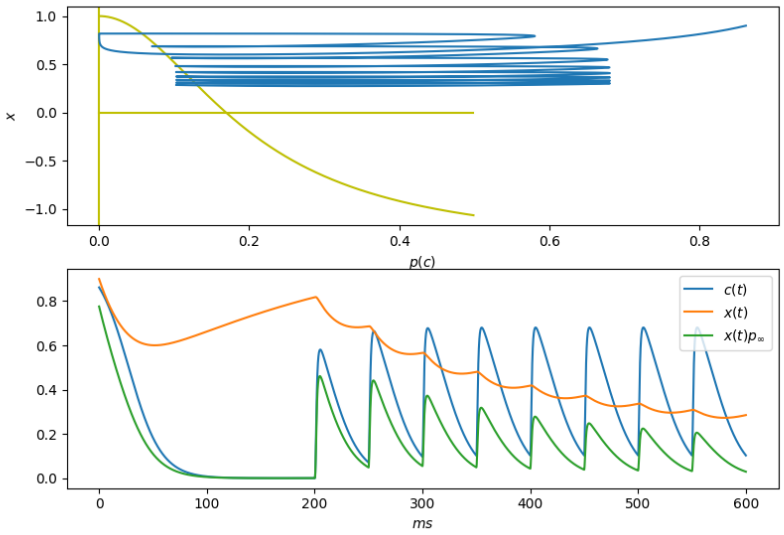

Figure 2: phase portrait and temporal courses of a depression configuration

Discrete and continuous nature of pre- and postsynaptic events. Regard one synaptic contact as the collection of all the synapses made by one presynaptic neuron onto a presynaptic neuron of interest.

Consider a synaptic contact formed by N synapses and assume that p is the average probability of activation for the synapses in the contact. If the average probability of release in a

(25)

Suppose there are C such presynaptic neurons with with N_1,...,N_C synapses, respectively. Assume that the number of vesicles in the RRP at the kth synapse from the jth neuron is n_{jk}, with $j \in \{1, ..., C\}$, $k \in \{1, ..., N_i\}$. If after a single action potential from neuron j, the probability of release at the kth synapse is p_{jk}, and vesicles are released independently at each synapse, then the average number of vesicles released at that synapse is $\hat{n}_{jk} = p_{jk} n_{jk}$. The time course of the normalized presynaptic neurotransmitter release is described by the product $q_{jk}(t)p_{jk}(t)$. The postsynaptic current at the jk-synapse is then

$$I(v_{jk}, t) = a_{jk} q_{jk}(t) p_{jk}(t) S\left(\frac{v_{jk}(t) - v_r}{v_T}\right) \tag{26}$$

where $v_{jk}$is the postsynaptic voltage, v_r is the reversal potential for the postsynaptic current, and v_T is the thermal potential[1]. S is a nonlinear function of v_{jk} that describes the electrodiffusive current in the open channel of the activated receptor and a_{jk} is the maximum amplitude of the postsynaptic current in the open channel that can be thought of as the product of the number of postsynaptic receptors and a conversion factor that transforms the normalized amount of neurotransmitter $q_{jk}p_{jk}$, into the proportion of active post-synaptic receptors at the jk-synapse. The peak amplitude of $I(v_{jk})$ causes a change in the postsynaptic potential that propagates and is modified throughout the propagation path. This postsynaptic current is a function of the amount of neurotransmitter released, the proportion of active receptors, and the postsynaptic membrane potential at the postsynaptic membrane.

Assuming that all the synapses are excitatory and that the postsynaptic neuron is at rest, let $\bar{v}_{jk}$ represent the peak postsynaptic potential at an integration site, say, the soma, resulting from the average release of neurotransmitter at the ij-synapse and the subsequent activation of the postsynaptic receptors. The peak in the voltage change that results from the average activation of the jth synaptic contact is then $\bar{v}_j$ which, at best, equals $\sum_{k=1}^{N_j} \bar{v}_{jk}$ when the peaks occur simultaneously at the soma. It is worth recalling that $\bar{v}_j$ is only the sum of the average voltage responses from all the synapses of the jth contact.

Assume that there is no noise, that p_{jk}, n_{jk}, and the jk-quanta q_{jk} are constant for $k \in \{1, ..., N_j\}$ and $j \in \{1, ..., C\}$, and also that the properties of the postsynaptic membrane along the path of propagation do not change for each combination of synaptic activations $jk_1, ..., jk_m$. Under such circumstances, the peak of the total propagated transients $\bar{v}_{jk_1} + ... + \bar{v}_{jk_m}$ can only take a finite number of values. However, even in such circumstances and given that a voltage transient can only reach a few millivolts in amplitude, and that the number of different combinations of activated synapses can be very large, then the idea of being able to distinguish discrete values related to the quanta released at the single synapses seems difficult, if not impossible. The quantal nature of the somatic postsynaptic potentials seems even more impossible to occur in consideration of the fact that each combination of synaptic activations is likely to activate voltage-gated channels along the integration path to different extents.

2.1 Current proportion between pre- and postsynaptic events due to difussion loss

[1] $v_T = kT/q$ where k is Boltzmann's constant, T is the absolute temperature, q is the elementary charge