3 state neurons for contextual processing

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Abstract

Neurons receive excitatory inputs via both fast AMPA and slow
NMDA type receptors. We find that neurons receiving input via
NMDA receptors can have two stable membrane states which are
input dependent. Action potentials can only be initiated from the
higher voltage state. Similar observations have been made in sev-
eral brain areas which might be explained by our model. The in-
teractions between the two kinds of inputs lead us to suggest that
some neurons may operate in 3 states: disabled, enabled and fir-
ing. Such enabled, but non-firing modes can be used to introduce
context-dependent processing in neural networks. We provide a
simple example and discuss possible implications for neuronal pro-
cessing and response variability.

1 Introduction

Excitatory interactions between neurons are mediated by two classes of synapses:
AMPA and NMDA, AMPA synapses act on a fast time scale ($\tau_{\text{AMPA}} \sim 5\text{ms}$), and
their role in shaping network dynamics has been extensively studied. The NMDA
type receptors are slow ($\tau_{\text{NMDA}} \sim 150\text{ms}$) and have been mostly investigated for
their critical role in the induction of long term potentiation, which is thought to be
the mechanism for storing long term memories. Crucial to this is the unique voltage
dependence of NMDA receptors [6] that requires both the presynaptic neuron to be
active and the post-synaptic neuron to be depolarized for the channel to open.
However, pharmacological studies which block the NMDA receptors impair a vari-
ety of brain processes, suggesting that NMDA receptors also play a role in shaping
the dynamic activity of neural networks [10, 3, 8, 11, 2].

Therefore, we wanted to examine the role of NMDA receptors in post-synaptic
integration. Harsch and Robinson [4] have observed that injection of NMDA con-
ductance that simulates synchronous synaptic input regularized firing while lower-
ing response reliability. Our initial observations using a minimal model with

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large NMDA inputs in a leaky dendrite showed a large regenerative depolarization. Neurons however, also possess a variety of potassium currents that are able to limit these large excursions in voltage. In particular, recent observations show that A-type potassium currents are abundant in dendrites of a variety of neurons [7]. Combining these potassium currents with random NMDA inputs showed that the membrane voltage alternated between two distinct subthreshold states. Similar observations of two-state fluctuations have been made in vivo in several cortical areas and the striatum [17, 9, 1]. The origin and possible functional relevance of these fluctuations have remained a puzzle. We suggest that the NMDA type inputs combined with potassium currents are sufficient to produce such membrane dynamics. Our results lead us to suggest that the fluctuations could be used to represent contextual modulation of neuronal firing.

2 NMDA-type input causes 2 state membrane fluctuations

2.1 Model

To examine the role of NMDA type inputs, we built a simple model of a cortical neuron receiving AMPA and NMDA type inputs. To capture the spatial extent of neuronal morphology we use a two-compartment model of pyramidal neurons [15]. We represent the soma, proximal dendrites and the axon lumped into one compartment containing the channels necessary for spike generation ($I_{Na}$ and $I_K$). The dendritic compartment includes two potassium currents, a fast activating $I_{KA}$ and the slower $I_{KS}$ along with a persistent sodium current $I_{NaP}$. The dendrite also receives synaptic input as $I_{NMDA}$ and $I_{AMPA}$.

The membrane voltage of the neuron obeys the current balance equations:

$$C_m \frac{dV_s}{dt} = -I_{Leak,i} - I_{Na,i} - I_{KDr,i} - \frac{g_c}{p}(V_s - V_i) - I_{syn},$$

while the dendritic voltage, $V_i$ obeys:

$$C_m \frac{dV_i}{dt} = -I_{Leak,i} - I_{NaP,i} - I_{KS,i} - I_{KA,i} - \frac{g_c}{1-p}(V_i - V_s) - I_{syn},$$

where $C_m$ is the specific membrane capacitance which is taken to be 1 μF/cm² for both the dendrite and the soma for all cells and $p = 0.2, g_c = 0.05$ determining the electrotonic structure of the neuron.

The passive leak current in both the soma and dendrites were modeled as $I_{Leak} = g_{leak}(V - E_{leak})$, where $g_{leak}$ was the leak conductance which was taken to be 0.3 mS/cm² for the soma and dendrite. $E_{leak} = -80$ mV was the leak reversal potential for both the compartments. The voltage-dependent currents were modeled according to the Hodgkin-Huxley formalism, with the gating variables obeying the equation:

$$\frac{dx}{dt} = \phi_x(\alpha_x(V)(1-x) - \beta_x(V)x) = \phi_x\left(\frac{x_{\infty}(V) - x}{\tau_x(V)}\right),$$
where $x$ represents the activation/inactivation gates for the voltage-dependent currents.

The sodium current, $I_{Na} = g_{Na}m_{\infty}^{3} h(V^{s} - E_{Na})$, where $g_{Na} = 45 \text{ mS/cm}^{2}$ and sodium reversal potential, $E_{Na} = 55 \text{ mV}$ with $m_{\infty}(V) = \frac{g_{m}(V)}{g_{m}(V) + \beta_{m}(V)}$. The activation variables, $\alpha_{m}(V) = -0.1\left(V + 32\right)/\exp\left(-(V + 32)/(10) = 1\right)$, $\beta_{m}(V) = 4\exp\left(-(V + 57)/18\right)$; $\alpha_{h}(V) = 0.07\exp\left(-(V + 48)/20\right)$ and $\beta_{h}(V) = 1/[\exp\left(-(V + 18)/(10) + 1\right)$, with $\phi_{m} = \phi_{h} = 2.5$.

The delayed rectifier potassium current, $I_{KDr} = g_{K}n^{4}(V^{s} - E_{K})$, where $g_{K} = 9 \text{ mS/cm}^{2}$ and potassium reversal potential, $E_{K} = -80 \text{ mV}$ with $n_{\infty}(V) = -0.01(V + 34)/\exp\left(-(V + 34)/(10) - 1\right), \beta_{n}(V) = 0.125\exp\left(-(V + 44)/(80)\right)$, with $\phi_{n} = 2.5$.

In the dendrite, the persistent sodium current, $I_{NaP} = g_{NaP}r_{\infty}^{3}(V^{s} - V_{Na})$, with $r_{\infty}(V) = 1/(1 + \exp\left(-(V + 57)/5\right))$ and $g_{NaP} = 0.25 \text{ mS/cm}^{2}$. The two potassium currents were $I_{Ks} = g_{K}s(V - V_{K})$, with $s_{\infty}(V) = 1/(1 + \exp\left(-(V + 50)/2\right))$ and $\tau_{s}(V) = 200/(\exp\left(-(V + 60)/10 + \exp\left((V + 60)/10\right)\right)$ and $g_{Ks} = 0.1 \text{ mS/cm}^{2}$; and $I_{KA} = g_{KA}a_{\infty}^{3}b_{\infty}(V - V_{K})$, with $a_{\infty}(V) = 1/(1 + \exp\left(-(V + 45)/6\right)), b_{\infty}(V) = 1/(1 + \exp\left(-(V + 56)/15\right))$ and $\tau_{b}(V) = 2.5(1 + \exp\left((V + 60)/30\right))$ and $g_{KA} = 10 \text{ mS/cm}^{2}$.

The NMDA current, $I_{NMDA} = f_{\text{NMDA}}(V - E_{\text{NMDA}})/(1 + 0.3|Mg|\exp\left(-0.06V\right))$, where $s$ was the activation variable and $f$ denoted the inactivation of NMDA channels due to calcium entry. AMPA and NMDA inputs were modeled as conductance kicks that decayed with $\tau_{AMPA} = 5 \text{ ms}$ and $\tau_{NMDA} = 150 \text{ ms}$. Calcium dependent inactivation of the NMDA conductance was modeled as a negative feedback $df/dt = (f_{\infty} - f)/2$, where $f_{\infty}$ was a shallow sigmoid function that was 1 below a conductance threshold of 2 mS/cm$^{2}$ and was inversely proportional to the NMDA conductance above threshold. The coupling conductance is $g_{c} = 0.1 \text{ mS/cm}^{2}$. The asymmetry between the areas of the two compartments is taken into account in the parameter $p = \text{somatic area}/\text{total area} = 0.2$. The temperature scaling factors are $\phi_{h} = \phi_{n} = 3.33$. Other parameter values are: $g_{leak} = 0.3$, $g_{Na} = 36$, $g_{K} = 6$, $g_{NaP} = 0.15$, $g_{Ks} = 1$, $g_{KA} = 50 \text{ mS/cm}^{2}$ unless otherwise noted; $E_{leak} = -75$, $E_{Na} = +55, E_{K} = -90, E_{KA} = -80 \text{ in mV}$. Synchronous inputs were modeled as a compound Poisson process representing 100 inputs firing at a rate $\lambda$ each spiking with a probability of 0.1. Numerical integration was performed with a fourth-order Runge-Kutta method using a 0.01 ms time step.

### 2.2 NMDA induced two-state fluctuations

Figure 1A shows the firing produced by inputs with high AMPA/NMDA ratio. Figure 1B shows that the same spike train input delivered via synapses with a high NMDA content results in robust two-state membrane behavior. We term the lower and higher voltage states as $UP$ and $DOWN$ states respectively. Spikes caused by AMPA-type inputs only occur during the up-state. In general, the same AMPA input can only elicit spikes in the postsynaptic neuron when the NMDA input switches that neuron into the up-state.

Transitions from down to up-state occur when synchronous NMDA inputs depolarize the membrane enough to cause the opening of additional NMDA receptor channels (due to the voltage-dependence of their opening). This results in a regenerative depolarization event, which is limited by the fast opening of $I_{KA}$-type