Dressed Neurons: Modeling Neural-Glial Interactions

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Abstract. Based on recent experimental data we design a model for neuronal membrane potentials that incorporates the influence of the surrounding glia (*dressed neurons*). Neurotransmitter released into the synaptic cleft triggers a Ca\(^{2+}\) response in nearby glial cells that spreads as a Ca\(^{2+}\) wave and interacts with other synapses via the release of glutamate from astrocytes. We consider the simple case of neuron-glial circuit that consists of a single neuron that triggers a Ca\(^{2+}\) response in the glial cell which in turn feeds back into synapses of the same neuron. It is shown that persistent spiking can occur if the glutamate receptors on the astrocytes are overexpressed - a condition that has been reported from patients suffering from mesial-lobe epilepsy.

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1. Neural-Glial Interactions

Neurons in most parts of the brain are outnumbered by glial cells by approximately a factor of 10. A realistic picture of brain tissue is therefore a mass of glial cells with embedded neurons. The most numerous type and best studied glial cells are the star-shaped astrocytes. Contrary to the long-time belief that the information processing in the brain is exclusively a task of the neurons, research in the recent years [13, 11, 3] has demonstrated that astrocytes listen to the neuronal chatter, respond to it and talk back to the neurons, thus modulating their functions. Astrocytes, in contrast to most neuronal cells, do not fire action potentials due to the lack of sufficient numbers of Na$^+$ channels [6]. Astrocytes do not connect to other astrocytes or neurons via long processes. Until recently it was believed that the role of the glia for brain function is to provide structural and chemical support for the neurons. Such support functions include for example the uptake of potassium after a neuronal action potential. Although it has been known for a long time that synaptic astrocytes respond with depolarization to neuronal action potentials, this was thought to be a response caused by the increased extracellular K$^+$ concentration. The discovery by Porter and McCarthy [13] that astrocytes respond to neuronal action potentials by binding glutamate to the metabotropic glutamate receptor has changed the current thinking about the role of astrocytes dramatically. It is now clear that astrocytes are active members of the neuroglial communication system and can modulate neuronal dynamics at the same synapse or synapses at some distance. As neurons fire, glutamate is released into the synaptic cleft, which is partially bound to the metabotropic glutamate receptors (mGluR) of the synaptic astrocytes. Metabotropic glutamate receptors are a subtype of glutamate receptors which are G-protein coupled and regulate a variety of intercellular signaling pathways. The group-I is a subtype of metabotropic glutamate receptors that is coupled to polyphosphoinoside hydrolysis. A particular kind of polyphosphoinoside, inositol 1,4,5-triphosphate (IP$_3$), acts as a second messenger and is a key player in the release of calcium from internal stores and regulates calcium signalling. Upon binding of glutamate to the astrocyte, IP$_3$ is released into the intracellular space of the synaptic astrocyte. IP$_3$ in turn binds to the IP$_3$ receptor in the endoplasmic reticulum (ER) and Ca$^{2+}$ is released from the ER into the cytosol. Such Ca$^{2+}$ release can occur in forms of intracellular Ca$^{2+}$ waves. The Ca$^{2+}$ wave can propagate across the cell membrane, through extracellular space into adjacent astrocytes. A sketch of this process is shown in Fig.1. It is important to note here that the processes of liberating Ca$^{2+}$ from internal stores is much slower than the time scale of the action potential, i.e. it is of the order of seconds.

An important question is, however, whether glial-processes can modulate neuronal synapses and thus the information processing in the brain. An important discovery towards the answer of this question is that an astrocytic Ca$^{2+}$ response is necessary and sufficient for the release of glutamate from astrocytes. Astrocytes with elevated Ca$^{2+}$ concentrations release glutamate into the extracellular space [11] that co-propagates with the Ca$^{2+}$ wave front. The co-propagating glutamate release can impact either the
same synapse the signal originated from or remote synapses. Synaptic transmission can be potentiated or inhibited by glutamate released from astrocytes. Presynaptic binding of glutamate to metabotropic glutamate receptors suppresses the release of vesicles and thus the amplitude of the postsynaptic excitatory or inhibitory responses. It has been directly demonstrated that the release of glutamate from astrocytes upon a Ca$^{2+}$ spike suppresses nearby synaptic transmission\cite{9}. On the other hand it has been shown that glutamate released from astrocytes can bind to postsynaptic NMDA receptors (ionotropic), leading to elevated neuronal Ca$^2+$ concentrations, increased frequency of miniature postsynaptic currents, and additional slow inward currents. Such a process results in positive feedback and reinforcement of the synapse. In Fig.2 we show a cartoon of the local synaptic processes involving the presynaptic neuron, the postsynaptic neuron and the synaptic astrocyte - hence the term “tripartite synapse” coined by Haydon et al.\cite{2}. The combined neural and glial system with multiple synapses and astrocytes interacting electrically and chemically over long-range and short range generates a rich dynamics which only very recently is being explored.

In this paper, we report on results on modeling the simplest possible neural-glial circuit, i.e. a single neuron, stimulated by a dc-current, coupled to an astrocyte. When the neuron exhibits an action potential, the synaptic astrocytes generates a Ca$^{2+}$ signal that feeds back onto another synapse of the same neuron. Given the extensive dendritic tree with its numerous synapses this is a realistic, yet simple circuit. We would like...
Figure 2. Upon firing of the presynaptic pyramidal neuron, glutamate (GLU) (blue circles) is released from the merging vesicles. GLU diffuses through the synaptic cleft and binds to (ionotropic) postsynaptic glutamate receptors (grayscale graded rectangles) and to the metabotropic glutamate receptors on the astrocyte (not depicted). The postsynaptic neuron exhibits an excitatory postsynaptic current (inset). The G-protein coupled metabotropic glutamate receptors in the membrane of the astrocytes generate the second messenger \( \text{IP}_3 \) in a cascade of biochemical reactions. \( \text{IP}_3 \) binds to \( \text{IP}_3 \) receptors in the membrane of the endoplasmic reticulum (ER), thereby activating the release of \( \text{Ca}^{2+} \) from the ER. As a consequence of the elevated intracellular \( \text{Ca}^{2+} \) concentration, the astrocyte releases GLU into the extracellular space. GLU can bind presynaptically to metabotropic glutamate receptors to inhibit release of vesicles thus inhibiting evoked transmission from the pre to the postsynaptic neuron. On the other hand the GLU released from astrocytes triggers more frequent postsynaptic depolarizing miniature events\[9\] thus enhancing the synapse.
to point out, however, that the role of astrocytes in brain function has many more aspects than those presented here. Calcium signals can be generated by excitatory and inhibitory synapses, they can travel through the tissue and affect and correlate remote synapses. The feedback to synapses can enforce and inhibit synapses depending on the expression levels of metabotropic and ionotropic glutamate receptors.

2. Pinsky - Rinzel Neuron Model for a Pyramidal Cell

The Pinsky - Rinzel Model (P-R) [12] is a two compartment model of a CA-3 pyramidal neuron and is a reduction of a complex 19-compartment cable-model by Traub [19]. The two compartments are phenomenological and describe the soma and the dendrites of a cell. The compartments are coupled to each other electrotonically with all fast currents for sodium spiking lumped in a soma-like compartment and the slower calcium and calcium mediated currents in a dendrite-like compartment. The original Traub-model describes three basic dynamical types of responses to either somatic or dendritic stimulation,

(i) Very low frequency bursting (< 8Hz) (VLF)
(ii) Low frequency bursting (8 – 20Hz) (LF )
(iii) Periodic Somatic Spiking.

The schematic diagram of the model is shown in Fig.3.

The conductance-based P-R model is described by the following set of ordinary differential equations (synaptic inputs (NMDA and AMPA) are excluded)

\[
C_m \frac{dV_s}{dt} = -I_{\text{Leak}}(V_s) - I_{\text{Na}}(V_s, h) - I_{\text{K-DR}}(V_s, n)
\]
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\[
C_m \frac{dV_d}{dt} = -I_{\text{Leak}}(V_d) - I_{\text{Caneous}}(V_d, s) - I_{\text{K-AHP}}(V_d, q) - I_{\text{K-C}}(V_d, C_{\text{neuron}}, c) + \frac{g_c}{1-p}(V_s - V_d) + \frac{I_d}{1-p},
\]

(1)

where \(V_s\) and \(V_d\) are the somatic and dendritic membrane potentials (in mV) measured with respect to a reference potential of \(-60mV\). \(I_s\) and \(I_d\) denote injected currents applied to the soma and dendrite divided by the total membrane area respectively and \(p\) is the ratio of the cell area occupied by soma and by the dendrites. The ionic currents are given by

\[
I_{\text{leak}}(V_s) = g_L(V_s - V_L)
\]

\[
I_{\text{leak}}(V_d) = g_L(V_d - V_L)
\]

\[
I_{\text{Na}} = g_{\text{Na}}m^2(V_s)h(V_s - V_{\text{Na}})
\]

\[
I_{\text{K-DR}} = g_{\text{K-DR}}n(V_s - V_K)
\]

\[
I_{\text{Caneous}} = g_{\text{Caneous}}s^2(V_d - V_{\text{Caneous}})
\]

\[
I_{\text{K-AHP}} = g_{\text{K-AHP}}q(V_d - V_K)
\]

\[
I_{\text{K-C}} = g_{\text{K-C}}c\chi([C_{\text{neuron}}])(V_d - V_K),
\]

(2)

where

\[
\chi([C_{\text{neuron}}]) = \min \left( \frac{[C_{\text{neuron}}]}{250.0}, 1.0 \right),
\]

(3)

and \(V_{\text{Na}}, V_K, V_{\text{Caneous}}\) denote the Nernst potentials of the sodium, potassium and calcium systems. The current \(I_{\text{astro}}\) describes feedback from the astrocytes to the neuron and will be discussed below. The kinetic equations for the gating variables \(h, n, s, c\) have the form

\[
\frac{dy}{dt} = \frac{y_\infty(U) - y}{\tau_y(U)},
\]

(4)

where

\[
U = \begin{cases} V_s & \text{if } y = h, n \\ V_d & \text{if } y = s, c \\ [C_{\text{neuron}}] & \text{if } y = q \end{cases}
\]

(5)

and

\[
y_\infty = \frac{\alpha_y}{\alpha_y + \beta_y} \quad \text{and} \quad \tau_y = \frac{1}{\alpha_y + \beta_y}
\]

(6)

with

\[
\alpha_m = \frac{0.32(13.1 - V_s)}{\exp\left((13.1 - V_s)/4\right) - 1} \quad ; \quad \beta_m = \frac{0.28(V_s - 40.1)}{\exp\left((V_s - 40.1)/5\right) - 1}
\]
\[
\alpha_n = \frac{0.016(35.1 - V_s)}{\exp((35.1 - V_s)/5) - 1}; \quad \beta_n = 0.25 \exp(0.5 - 0.025V_s)
\]
\[
\alpha_h = 0.128 \exp((17 - V_s)/18); \quad \beta_h = \frac{4}{1 + \exp((40 - V_s)/5)}
\]
\[
\alpha_s = \frac{0.0002}{\exp((-0.072(V_d - 65))}; \quad \beta_s = \frac{0.02(V_d - 51.1)}{\exp((V_d - 51.1)/5) - 1}
\]
\[
\alpha_c = \begin{cases} 
    (\exp((V_d - 10)/11 - (V_d - 6.5)/27))/18.975 & \text{for } V_d < 50mV \\
    2 \exp((6.5 - V_d)/27) & \text{for } V_d > 50mV 
\end{cases}
\]
\[
\beta_c = \begin{cases} 
    2 \exp((6.5 - V_d)/27) - \alpha_c & \text{for } V_d < 50mV \\
    0 & \text{for } V_d > 50mV 
\end{cases}
\]
\[
\alpha_q = \min(0.00002[Ca_{\text{neuron}}], 0.01) ; \quad \beta_q = 0.001.
\]

Finally \([Ca_{\text{neuron}}]\) denotes the dimensionless intracellular free calcium level in the dendritic compartment

\[
\frac{d[Ca_{\text{neuron}}]}{dt} = -0.13I_{Ca} - 0.075[Ca_{\text{neuron}}].
\]

Finally \([Ca_{\text{neuron}}]\) denotes the dimensionless intracellular free calcium level in the dendritic compartment

\[
\frac{d[Ca_{\text{neuron}}]}{dt} = -0.13I_{Ca} - 0.075[Ca_{\text{neuron}}].
\]

Currents, conductances and capacitance are in units of \(\mu A/cm^2\), \(mS/cm^2\) and \(\mu F/cm^2\) respectively, while time is measured in \(ms\).

To complete the model, we use experimental data that relate the \(Ca^{2+}\) concentration in the astrocytic environment to additional slow synaptic inward currents in adjacent neurons[1]. The recordings were made from a single neuron grown on microislands of astrocytes and can be fitted by the function of inward current versus astrocytic \(Ca^{2+}\) concentration.

\[
I_{\text{astro}} = 2.11 \Theta(\ln y) \ln y
\]
\[
y = [Ca^{2+}] - 196.69,
\]

with the Heaviside function \(\Theta(x)\). The recorded total current (measured in pA) was converted to a current density measured in \(\mu A/cm^2\) by assuming a spherical soma.

The standard values listed in table 1 for the parameters of the Pinsky-Rinzel model were used: At these standard values the stable rest state at the rheobase of \(I_s = -0.3\mu A/cm^2\) are \(V_s = -4.6mV, V_d = -4.5mV, h = 0.999, n = 0.001, s = 0.009, c = 0.007, q = 0.010\) and \([Ca_{\text{neuron}}] = 0.2\mu M\).

Similar as in Traub’s model the R-P model has a slight negative rheobase of \(I_s = -0.3\mu A/cm^2\). When \(I_s\) is increased there is transition from rest to VLF-bursting to somatic spiking. For currents between \(-0.25\mu A/cm^2\) and \(+1.25\mu A/cm^2\), inter-burst frequencies of 0.3 hz to 4 hz are observed. Aperiodic behavior is observed for intermediate current values from \(1.5\mu A/cm^2\) to \(2.0\mu A/cm^2\). Somatic spiking begins at \(I_s = 2.25\mu A/cm^2\). A stable state of depolarization \((V_s = 33.3mV)\) is reached at \(I_s = 22.5\mu A/cm^2\).

In Fig.5 we show a bifurcation diagram of the Pinsky-Rinzel model as the somatic current \(I_s\) is increased.
Figure 4. Simultaneous recordings (data from fig 5-B [11]) of astrocytic calcium and total inward current in the neuron are shown by open circles while the fit by Eq.9 is shown as a solid curve.

Table 1. Parameter values for Pinsky-Rinzel Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( g_L )</td>
<td>0.1 ( mS/cm^2 )</td>
</tr>
<tr>
<td>( g_{Na} )</td>
<td>30.0 ( mS/cm^2 )</td>
</tr>
<tr>
<td>( g_{K-DR} )</td>
<td>15.0 ( mS/cm^2 )</td>
</tr>
<tr>
<td>( g_{Ca} )</td>
<td>10.0 ( mS/cm^2 )</td>
</tr>
<tr>
<td>( g_{K-AHP} )</td>
<td>0.8 ( mS/cm^2 )</td>
</tr>
<tr>
<td>( g_{K-C} )</td>
<td>15.0 ( mS/cm^2 )</td>
</tr>
<tr>
<td>( V_{Na} )</td>
<td>115.0 mV</td>
</tr>
<tr>
<td>( V_{Ca} )</td>
<td>140.0 mV</td>
</tr>
<tr>
<td>( V_K )</td>
<td>-15.0 mV</td>
</tr>
<tr>
<td>( V_L )</td>
<td>0.0 mV</td>
</tr>
<tr>
<td>( g_c )</td>
<td>2.1 ( mS/cm^2 )</td>
</tr>
<tr>
<td>( p )</td>
<td>0.5</td>
</tr>
<tr>
<td>( C_M )</td>
<td>3.0 ( \mu F/cm^2 )</td>
</tr>
</tbody>
</table>
Figure 5. Bifurcation diagram of the Pinsky-Rinzel model as the somatic input current $I_s$ is varied. The star denotes the rheobase $I_{rheo}$, i.e., the offset current to keep the neuron from oscillating. For $I < I_{rheo} = -0.3\,\mu A/cm^2$ the neuron does not oscillate spontaneously. Very low frequency bursts are observed right above rheobase. Somatic spiking occurs for $I > 2.25\,\mu A/cm^2$. For oscillatory states the minimum and maximum amplitude of the oscillations are plotted.

Similarly for dendritic input via $I_d$ the transition is from rest to VLF bursting to LF bursting, no somatic spiking in the regime of standard parameters is observed. For $I_d$ in the range of $-0.25\,\mu A/cm^2$ to $2.0\,\mu A/cm^2$, VLF bursts of frequencies less than 7Hz are observed. At slightly higher $I_d > 2.25\,\mu A/cm^2$ chaotic and aperiodic patterns are observed. A stable rest state is attained at $I_d = 100.0\,\mu A/cm^2$.

In summary, rich dynamical behavior that includes periodic bursting, complex bursting, somatic spiking and aperiodic spiking is observed over a large range of frequencies and can account for most of the behavioral repertoire of the original model by Traub [19] and CA3 pyramidal neurons.

3. Calcium signaling in astrocytes

When a neuron fires, it releases quantal amounts of neurotransmitters into the synaptic cleft [17]. As neurotransmitters bind to the mGluRs on the astrocytes, triggering the release of IP$_3$ intracellularly, we assume that this amount is also quantized. The
production of intracellular IP$_3$ in the astrocyte is modeled by
\[
\frac{d[I_{P_3}]}{dt} = \frac{1}{\tau_{I_{P_3}}}(I_{P_3}^* - [I_{P_3}]) + r_{I_{P_3}}\Theta(v - 50mV),
\] (10)
where $[I_{P_3}]^*$ is the equilibrium concentration of IP$_3$. We use here the recently determined values $[21]$ of $\tau_{I_{P_3}} = 0.000140 \text{ ms}$ and $[I_{P_3}]^* = 160.0nM$, respectively. The parameter $r_{I_{P_3}}$ determines the rate of IP$_3$ production in response to a neuronal action potential. The production term is activated when the membrane potential of the neuron is larger than $+50mV$ via the Heavyside function $\Theta(x)$. Since the production of intracellular IP$_3$ is proportional to the activated mGluRs, the parameter $r_{I_{P_3}}$ is proportional to the abundance of mGluRs in the membrane of the synaptic astrocytes.

Production of IP$_3$ in the intracellular space of astrocytes triggers the release of Ca$^{2+}$ from internal stores, most notably the endoplasmic reticulum (ER). This process has been modeled intensively over the last 10 years or so (for a recent review, see $[15]$). The cytosolic Ca$^{2+}$ concentration can change due to Ca$^{2+}$ flux from the ER through the IP$_3$ release channels, leakage flux from the ER into the cytosol, and pump-flux from the cytosol into the ER and transport of Ca$^{2+}$ through the cell membrane which is not taken into account here. We choose the Li-Rinzel model $[14]$, where the Ca$^{2+}$ concentration in the intracellular space is described by the set of two equations
\[
\frac{d[Ca^{2+}]}{dt} = -J_{\text{Channel}}(q) - J_{\text{Pump}} - J_{\text{Leak}}
\] (11)
\[
\frac{dq}{dt} = \alpha q(1 - q) - \beta q,
\] (12)
where $J_{\text{Channel}}$ denotes the calcium flux from the ER to the intracellular space through the IP$_3$R channel, $J_{\text{Pump}}$ the calcium flux pumped from the intracellular space into the ER, and $J_{\text{Leak}}$ the leakage flux from the ER to the intracellular space. The expressions for the fluxes are given by
\[
J_{\text{Channel}} = c_1v_1m_{\infty}n_{\infty}q^3([Ca^{2+}] - [Ca^{2+}]_{ER})
\]
\[
J_{\text{Pump}} = \frac{v_3[Ca^{2+}]^2}{k_3^2 + [Ca^{2+}]^2}
\]
\[
J_{\text{Leak}} = c_1v_2([Ca^{2+}] - [Ca^{2+}]_{ER}),
\] (13)
with
\[
m_{\infty} = \frac{[IP_3]}{[IP_3] + d_1} ; \quad n_{\infty} = \frac{[Ca^{2+}]}{[Ca^{2+}] + d_5}
\]
\[
\alpha_q = a_2d_2\frac{[IP_3] + d_1}{[IP_3] + d_3} ; \quad \beta_q = a_2[Ca^{2+}].
\] (14)

The parameters of the model are given in table2.

Conservation of Ca$^{2+}$ within the cell implies the constraint $[Ca^{2+}]_{ER} = (c_0 - [Ca^{2+}])/c_1$ with $c_0 = 2.0 \mu M$.

This simplified model resembles the Hodgkin-Huxley model for electrically excitable membranes if the concentration $[Ca^{2+}]$ is replaced by the transmembrane potential. The driving force for Ca$^{2+}$ fluxes is the concentration gradient $([Ca^{2+}] - [Ca^{2+}]_{ER})$.
Table 2. Parameter values for Pinsky-Rinzel Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c_1$</td>
<td>0.185</td>
</tr>
<tr>
<td>$v_1$</td>
<td>6/s</td>
</tr>
<tr>
<td>$v_2$</td>
<td>0.11/s</td>
</tr>
<tr>
<td>$v_3$</td>
<td>0.9/(Ms)</td>
</tr>
<tr>
<td>$k_3$</td>
<td>0.1µM</td>
</tr>
<tr>
<td>$d_1$</td>
<td>0.13µM</td>
</tr>
<tr>
<td>$d_2$</td>
<td>1.049µM</td>
</tr>
<tr>
<td>$d_3$</td>
<td>0.9434µM</td>
</tr>
<tr>
<td>$d_5$</td>
<td>0.08234µM</td>
</tr>
<tr>
<td>$a_2$</td>
<td>0.2/µMs</td>
</tr>
</tbody>
</table>

the driving force for the ionic currents in the Hodgkin-Huxley equation is the voltage gradient. Eqs.10-14 predict that stimulation of astrocytes with glutamate released into the synaptic cleft triggers intracellular astrocytic Ca$_{2+}$ signals. This prediction is well-described in the literature, in vitro [8] and in vivo[5].

In the absence of neuronal stimulus, i.e. $[IP_3] = [IP_3]^*$, Eq.6-9 predict Ca$_{2+}$ oscillations for 0.345µM < $[IP_3]$ < 0.644µM and steady states otherwise. The transitions from steady-state to oscillations and from oscillations to steady state are due to supercritical Hopf bifurcations. Ca$_{2+}$ oscillations are frequently observed in astrocytes, hepatocytes, pancreatic island cells, and various types of epithelia. In our model, the concentration of IP$_3$ in the astrocytes is controlled by neuronal firing and thus becomes another dynamic variable.

4. Neuron in contact with single astrocyte

We now combine the Pinsky-Rinzel model for the neuron with the model for Ca$_{2+}$ in the astrocytes, where we assume that the additional inward currents to the neuron triggered by Ca$_{2+}$ in nearby astrocytes are somatic, averaging over many synapses. An important parameter is the production rate $r_{IP_3}$ of IP$_3$, in Eq.10. If $r_{IP_3} = 0$, IP$_3$ will approach its small equilibrium value and the calcium dynamics in the astrocyte is decoupled from the neuron. Thus, the neuron behaves as described by the Pinsky Rinzel model. The bifurcation diagram as the somatic input is increased is shown in Fig.5. When the IP$_3$ production is nonzero, i.e. the astrocyte is now encoding the neuronal information, the bifurcation diagram is changed (see Fig.6).

Most important, the oscillating branches continue well below the former rheo-base, where now the fixed point coexists with spontaneous oscillations. This means that the dressed neuron is more likely to spontaneously oscillate with smaller stimuli. In Figs.7 we display the time course of the neuronal action potential, the intracellular Ca$_{2+}$ concentration in the astrocyte, and the concentration of IP$_3$ in the astrocyte. The neuron
**Figure 6.** Bifurcation diagram of the coupled neuron-astrocyte model with an IP$_3$ production rate of 1.0$\mu$M/s with a rheobase of $-0.3\mu$A/cm$^2$. Starting from small somatic currents, the model approaches a stationary somatic membrane potential (branch a). Increasing $I_s$ beyond the rheobase leads to very-low frequency bursting (minima and maxima of the membrane potential $V_S$ are denoted by branches (b) and (c)). Further increase of $I_s$ results in somatic spiking (branches (d) and (e) denote the minimum and maximum of the somatic membrane potential). Decreasing $I_s$, the neuron remains in the state of somatic firing (((d) and (e)) even below the rheobase. Somatic spiking terminates at a current of $I_s < -2\mu$A/cm$^2$.

is stimulated by a constant current which is large enough to trigger somatic spiking. The stimulation is terminated after 10s (arrow). During this time, the concentration of IP$_3$ and Ca$^{2+}$ builds up in the astrocyes (with possible calcium oscillations). As the stimulation is terminated, the spiking of the membrane potential terminates. As the IP$_3$ production rate is increased, the neuron keeps firing after termination of the stimulus (see Fig.8). This spiking is triggered by the slow neuronal inward currents induced by the elevated Ca$^{2+}$ in the the astrocyte. The spiking stops when the degradation of IP$_3$ overwhelmes the production of IP$_3$. Further increase of the production rate of IP$_3$ leads to the situation where IP$_3$ production overwhelmes IP$_3$ degradation leading to sustained spiking after termination of stimulation (see Fig.9).
Figure 7. In the upper panel the neuronal membrane potential (soma compartment) is shown. The stimulation is terminated after 10s (see arrow). Shortly after termination of the stimulus, the neuron falls back into its resting state. In the lower panel, the concentrations of IP$_3$ and Ca$^{2+}$ are shown as function of time. As the neuron fires, the concentration of IP$_3$ builds up and decays (due to degradation) as the neuron stops firing. The Ca$^{2+}$ concentration increases only slightly during the time the neuron fires. The IP$_3$ production rate in this figure is 0.5 µM/s.

5. Summary and Conclusions

We have put forward a model for the dynamics of the membrane potential of a cortical neuron in contact with an astrocyte. Release of glutamate during an action potential triggers a calcium spike in the synaptic astrocyte that propagates through the astrocyte and potentiates other synapses on the dendritic tree through the release of glutamate. The neuron is modeled using a reduction of Traub’s model. The coupling of the astrocytic calcium response to additional synaptic inward currents is matched to experimental data. For the lack of quantitative data, the relation between the released glutamate from the synapse and the production of the second messenger IP$_3$ has been chosen linear. An interesting situation occurs when a large production rate $r_{IP_3}$ of IP$_3$ is used. A large production rate of IP$_3$, is the consequence of overexpressed metabotropic glutamate receptors as it has been reported in astrocytes from epileptic foci of humans suffering from mesial lobe epilepsy [18, 20, 4]. Our model predicts an enhanced astrocytic Ca$^{2+}$ response in such a situation (compare Figs.7 and Fig.8), consistent with the observation of increased IP$_3$ hydrolysis and Ca$^{2+}$ response in astrocytes during epileptic
Figure 8. In the upper panel the neuronal membrane potential (soma compartment) is shown. The stimulation is terminated after 10s (see arrow). In the lower panel, the concentrations of IP$_3$ and Ca$^{2+}$ are shown as function of time. As the neuron fires, the concentration of IP$_3$ builds up. The Ca$^{2+}$ concentration - as its dynamics is much slower than neuronal dynamics - spikes after the stimulation of the neuron is terminated. Thus the astrocytic feedback keeps the neuron firing although the stimulus is terminated. When the Ca$^{2+}$ oscillation swings to lower astrocytic Ca$^{2+}$ levels (Ca$^{2+}$ is taken up by the ER), the IP$_3$ concentration drops and the somatic spiking stops. The IP$_3$ production rate for this figure is 1.0µM/s.

seizures[10, 16]. Our model indeed predicts that for a large production rate of IP$_3$ (overexpressed metabotropic glutamate receptors) in response to neuronal firing the neuron can be switched to an oscillatory state through long-lasting stimulation of the neuron, mimicking an epileptic state. Enhanced astrocytic Ca$^{2+}$ response in epileptic tissue and feedback to the neuron has also been reported in [7]. Slice studies have revealed that in pyramidal cells from hyperexcitable regions with more Ca$^{2+}$ active astrocytes there is a high-level of spontaneous excitatory neuronal activity[7] which in few cases become epileptic bursts. Another important observation is that high levels of astrocytic glutamate release trigger trains of action potentials in nearby neurons (in culture)[1]. In summary, our model for a neuron in contact with an astrocyte, predicts epilepsy-type neuronal spiking for overexpressed metabotropic glutamate receptors. Although direct evidence for this novel mechanisms for epilepsy does not exists there is convincing similarity between model predictions and experimental observations.
Figure 9. In the upper panel the neuronal membrane potential (soma compartment) is shown. The stimulation is terminated after 10s (see arrow). The difference to Fig.8 is that the larger $IP_3$ production rate of $1.5 \mu M/\text{s}$ does not let the $Ca^{2+}$ concentration decrease beyond the level where it ceases to feed back to the neuron. The neuronal spiking with a frequency of about $90 Hz$.

References


