Research Article

Depolarization block of interneurons

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In this paper we study the behavior of an hippocampal interneuron model. The mathematical model is the usual Hodgkin-Huxley model modified to reproduce the electrophysiology of these fast-spiking neurons. The synaptic input current is modeled in two ways, one is deterministic the other one is a stochastic process depending on random events. Our results proved that, in presence of large depolarizing input currents, the system undergoes a depolarization block, a phenomenon that has been observed in other kind of neurons. This is an important mechanism which stops sustained neural activity when a neuron receives a strong excitation. However, numerical simulations showed that an inhibitory synaptic current can reactivate neural activity when synaptic current and depolarizing current are a in given interval. We argue that including such mechanism in mathematical models of interneurons can have a significant impact in the study of epilepsy and other uncontrolled activity of the neurons.

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Introduction

In this paper we reveal the presence of depolarization block in a model of hippocampal interneuron. In whole generality the term interneuron is referred to a GABAergic non-principal neuron ([1]). Whereas principal cells (such as the pyramidal cells in the CA1 region of the hippocampus) have long axons which project processed signals to other regions of the brain and form excitatory synapses (i.e. synapses mediated by NMDA and AMPA receptors using glutamate as neurotrasmitter), interneurons usually have short axons and a dendritic tree which lays in the same region where the cellular body rests and mainly plays an inhibitory role (synapses mediated by GABAa or GABAb receptors using gamma-aminobutyric acid - GABA - as neurotrasmitter). Their function in biological neural network is to balance excitation

and control the precise spike timing of target neurons, synchronizing in this way the spiking activity of large populations of cells ([2]). This last function in particular, is involved in the synaptic plasticity process which is the base for memory formation and in the generation of oscillatory network patterns such as gamma waves or the characteristic hippocampal theta rhythm.

When we speak about interneurons we should point out that the terminology which is used to refer to them can vary a lot depending on which characteristics the author focuses his attention on (morphological, neurochemical, physiological etc.). Nevertheless the functional role in the local circuitry of an interneuron has been proposed as the best identifying criterium ([3]). In this paper we follow the terminology used by the authors who proposed and used considered model ([4],[5]).

The block of neural activity has different causes which depend on the system of neurons where it has been observed. One important system is the CA1 neurons of the Hippocampus. The increase of the applied current increases the spiking frequency and for a certain value the neurons stop firing. It is a phenomenon different from the usual Hopf bifurcation where the amplitudes of the oscillations of the potentials goes to zero for an increasing current. In the depolarization block there is no such a decrease but the spikes simply stop. The presence of depolarization block in interneurons is remarkable as the block of the activity of an interneuron due to a sustained excitation could blow up the complex mechanism of memory formation which strongly relies on their functioning (see for example the role of interneurons in a model of realistic hippocampal neural network implemented in [6]). In addition, depolarization block occurring in paravalbumin-expressing fast-spiking interneuron has recently been proposed has a possible cause of focal epileptic seizure propagation ([7]). Finally, the analysis of interneurons activity is particularly interesting as the computational study of depolarization block in such neurons has never, at the best of our knowledge, been intensively developed.

In this paper we perform a computational study of a simple, yet paradigmatic, mathematical model of fast-spiking basket interneuron. Bifurcation of the model with respect to the depolarizing input current were investigated, along with the influence of a coupled inhibitory synaptic current.

Materials and Methods

In this work we considered the model of a basket interneuron used in the neural network studied in [4] and previously presented in [5]:

$$\begin{cases} C\frac{dV}{dt} &= I_{ext} - I_L(V) - I_{Na}(V,h) - I_K(V,n) - I_{syn} \\ \frac{dh}{dt} &= \phi_h[\alpha_h(V)(1-h) - \beta_h(V)h] \\ \frac{dn}{dt} &= \phi_n[\alpha_n(V)(1-n) - \beta_n(V)n]. \end{cases} \quad (1)$$

In this system the leakage current is

$$I_L(V) = \bar{g}_L(V - E_L),$$

the sodium current is

$$I_{Na}(V,h) = \bar{g}_{Na}[m_\infty(V)]^3 h(V - E_{Na}),$$

where the function involved in the dynamic of the variable h are

$$\alpha_h(V) = 0.07\exp\big(-\frac{V+58}{20}\big),$$
$$\beta_h(V) = \frac{1}{\exp\big(-0.1(V+28)\big)+1},$$

whereas

$$m_\infty(V) = \frac{\alpha_m(V)}{\alpha_m(V)+\beta_m(V)},$$

where

$$\alpha_m(V) = -0.1\frac{V+35}{\exp\big(-0.1(V+35)\big)-1},$$
$$\beta_m(V) = 4\exp\big(-\frac{V+60}{18}\big).$$

Finally, the delayed rectifier potassium current is given by

$$I_K(V,n) = \bar{g}_K n^4(V - E_k),$$

where

$$\alpha_n(V) = -0.01\frac{V+34}{\exp\big(-0.1(V+34)\big)-1},$$
$$\beta_n(V) = 0.125\exp\big(\frac{V+44}{80}\big).$$

We notice that this basket cell model has the form of a Hodgkin-Huxeley model in which the activation variable of the sodium current m is replaced by its asymptotic value $m_\infty(V)$. This corresponds to assume that the dynamic of this variable is much quicker than that one of the inactivation variables h and n. The values of the parameters which define the dynamic are summarized in Table 1.

Parameter	Value	Unity of measure
C	1	$\frac{\mu \mathrm{F}}{\mathrm{cm}^2}$
$\bar{g}_L$	0.1	$\frac{\mathrm{mS}}{\mathrm{cm}^2}$
E_L	-65	mV
$\bar{g}_{Na}$	35	$\frac{\mathrm{mS}}{\mathrm{cm}^2}$
E_{Na}	-55	mV
$\bar{g}_K$	9	$\frac{\mathrm{mS}}{\mathrm{cm}^2}$
E_K	-90	mV
ϕ_h	5	-
ϕ_n	5	-

Table 1. Parameter set of system 1

In order to detect the bifurcations which this model undergoes when the applied current is varied (and $I_{syn} = 0$), the MatCont continuation package ([8]) has been used.

In addition, we analyzed the influence of an external inhibitory synaptic current mediated by GABAa receptors. Two different models were considered for this inhibitory current, a deterministic model and a stochastic one. In the first case we considered a deterministic model proposed by Wang and Buzsáki [5] which needs the simulation of the membrane potential time course of the presynaptic cell, i.e. implementation of a presynaptic neuron model. In this case the synaptic current is given by

$$I_{syn}(V, s) = \bar{g}_{syn} s (V - E_{syn})$$

where $\bar{g}_{syn}$ is the maximal synaptic conductance, E_{syn} is the reverse potential of the synaptic current and s is the activation state variable representing the fraction of open ionic channels. The dynamic equation for variable s is given by

$$\frac{ds}{dt} = \alpha F(V_{pre})(1 - s) - \beta s.$$

We remark that in this equation the presynaptic potential V_{pre} is involved in the sigmoid function

$$F(x) = \frac{1}{1 + \exp(\frac{x - \theta_{syn}}{K})}.$$

In these simulations a basket cell with a 100 Hz firing frequency (in the gamma range) has been used as the presynaptic cell. The synaptic parameters are summarized in
Table 2.

Parameter	Value	Unity of measure
E_{syn}	-80	mV
α	10	ms^{-1}
β	0.07	ms^{-1}
θ_{syn}	0	mV
K	2	mV

Table 2. Synaptic values corresponding to a GABAa-mediated current in the case of deterministic model. Source [4].

In the second case, a stochastic model for the synaptic current was considered:

$$I_{syn}(t, V; \{t_i\}) = g_{syn}(t; \{t_i\})(V - E_{syn}),$$

where the $\{t_i\}$ is a stochastic process representing the spike times of the presynaptic cell (i.e. the instants in which the presynaptic cell fires an action potential). In our simulations this process is generated in the following way: we consider N Gaussian distributed random variables T_i for $i = 1, \dots, N$, each one representing the i-th interspike interval, i.e. the time gap between the $(i-1)$-th presynaptic action potential and the i-th one. Then we fix $t_0 = 0$ and $t_i = t_{i-1} + T_i$ for $i = 1, \dots, N$. In order to reproduce the 100 Hz firing frequency of the presynaptic cell, the mean of the Gaussian distribution has been fixed to $\mu = 10\mathrm{ms}$ and the variance to $\sigma^2 = 0.1\mathrm{ms}^2$.

For implementing a linear postsynaptic summation, the synaptic conductance is given as a sum of normalized double exponential functions:

$$g_{syn}(t;\{t_i\}) = \sum_i \bar{g}_{syn} f(t-t_i),$$

where $\bar{g}_{syn} f(t-t_i)$ is the contribution to the synaptic current given by the i-th presynaptic action potential and

$$f(x) = \begin{cases} \bar{f}\left(\exp\left(-\frac{x}{\tau_{fall}}\right) - \exp\left(-\frac{x}{\tau_{rise}}\right)\right) & x \geq 0 \\ 0 & x < 0. \end{cases}$$

In this expression the normalization constant

$$\bar{f} = \frac{1}{\exp\left(-\frac{\tau_{rise}}{\tau_{rise}-\tau_{fall}}\ln\left(\frac{\tau_{rise}}{\tau_{fall}}\right)\right) - \exp\left(-\frac{\tau_{fall}}{\tau_{rise}-\tau_{fall}}\ln\left(\frac{\tau_{rise}}{\tau_{fall}}\right)\right)}$$

is such that $f(x_{max}) = 1$ whereas τ_{rise} and τ_{fall} are temporal constants influencing the rising and falling phase of the synaptic current respectively ([9]) and their values, together with the value of E_{syn} are summarized in

Table 3.

Parameter	Value	Unity of measure
E_{syn}	-75	mV
τ_{rise}	1	ms
τ_{fall}	8	ms

Table 3. Synaptic values corresponding to a GABAa-mediated current in the case of stochastic model. Source [6].

This double exponential form has been firstly proposed by Destexhe et al. ([10]) and it reproduces the time course of real synaptic currents.

All simulations were performed on a Intel i7 quad-core processor with 4 GB of RAM running on Windows 7 using MatLab.

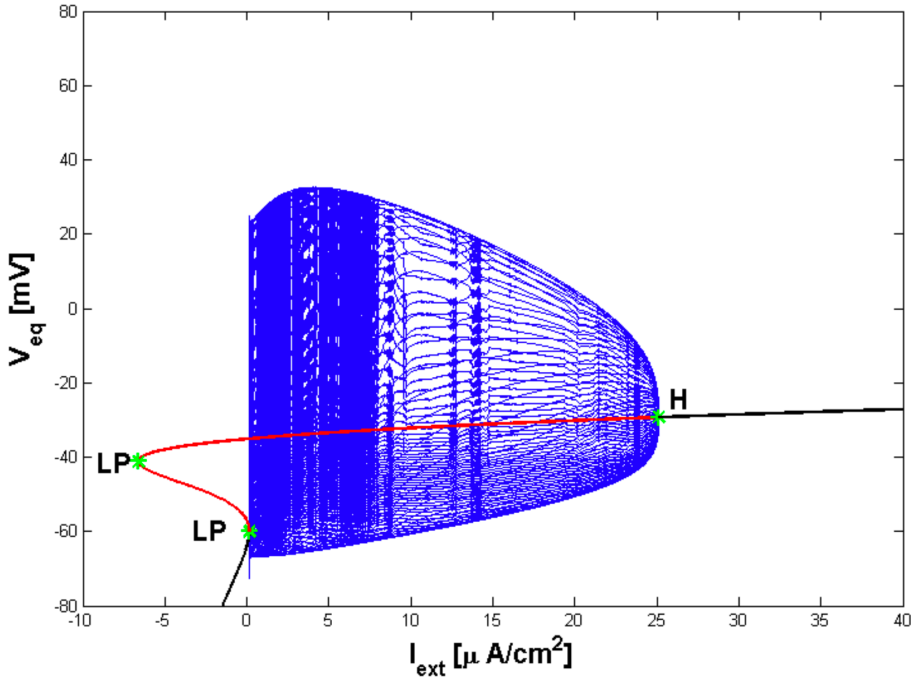

Figure 1.Bifurcation diagram of the equilibrium of the basket cell model with I_{ext} as bifurcation parameter. The equilibrium is stable where the line is black and it is unstable where the line is red, whereas the blue line indicates a stable limit cycle. Non hyperbolic equilibria are marked in green and the label `H` denotes a supercritical Andronov-Hopf bifurcation and `LP` a saddle node bifurcation.

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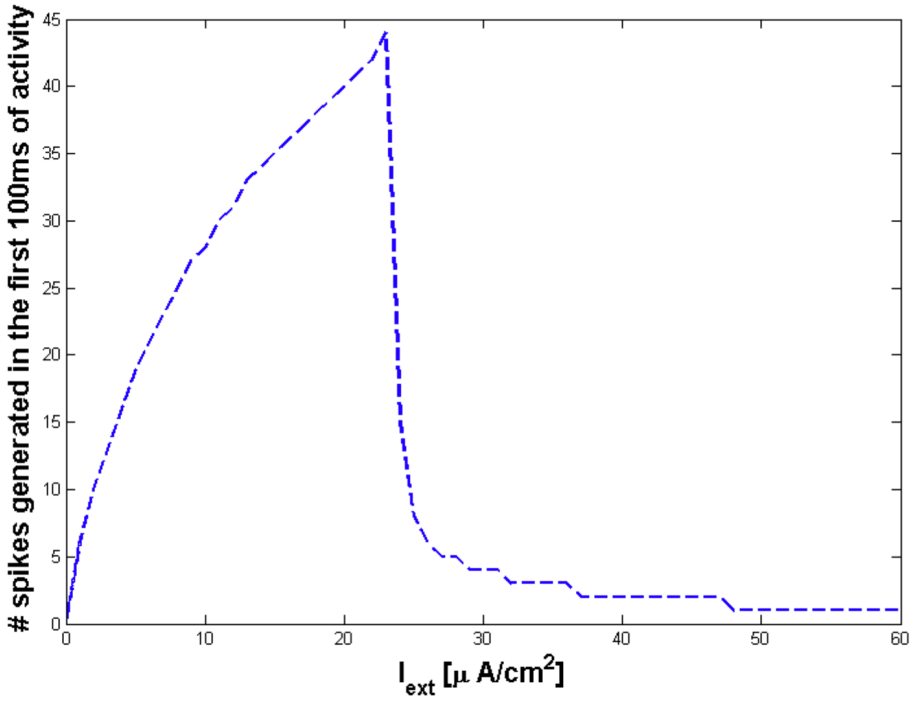

Figure 2. Action potential generated in the firsts 100 ms of activity of the basket cell as a function of the applied current I_{ext}

Results

In the model of basket interneuron, when we investigated the bifurcations occurring using I_{ext} as bifurcation parameter, we found an equilibrium undergoing a supercritical Andronov-Hopf bifurcation for a large value of this parameter ($I_{ext} \cong 25.13 \frac{\mu A}{cm^2}$) and two saddle-node bifurcations for $I_{ext} \cong 0.16 \frac{\mu A}{cm^2}$ and $I_{ext} \cong -6.58 \frac{\mu A}{cm^2}$ respectively (Fig. 1). Qualitatively speaking, we observed that when $I_{ext} \in [0.16 \frac{\mu A}{cm^2}, 25.13 \frac{\mu A}{cm^2}]$ the equilibrium is unstable and the solutions tends to a globally attracting limit cycle surrounding it. In this situation the neuron emits an infinite train of action potentials. On the other hand, for $I_{ext} < 0.16 \frac{\mu A}{cm^2}$ and $I_{ext} > 25.13 \frac{\mu A}{cm^2}$ the orbits are attracted by the stable equilibrium and then the neuron is silent.

Among the described bifurcations, the most interesting one is the Andronov-Hopf bifurcation as it represents the presence of a depolarization block in the basket interneuron. In fact, in Figure 2, we can see that the number of action potential generated in the first 100 ms progressively increases when augmenting the input current I_{ext} but it eventually drops down when it approaches the value $25.13 \frac{\mu A}{cm^2}$.

This picture also implies that this neuron belongs to Hodgkin's excitability Class 1, the class of neurons that can exhibit action potentials with arbitrarily low frequency. According to E. Izhikevich ([11]) this class of neural excitability is due to the presence of a saddle node bifurcation on invariant circle, and this is the case in our model too. In fact, further graphical investigation (not shown here) showed that the saddle-node bifurcation occurring for $I_{ext} \cong 0.16 \frac{\mu A}{cm^2}$ is indeed on the invariant circle corresponding to sustained neuronal activity.

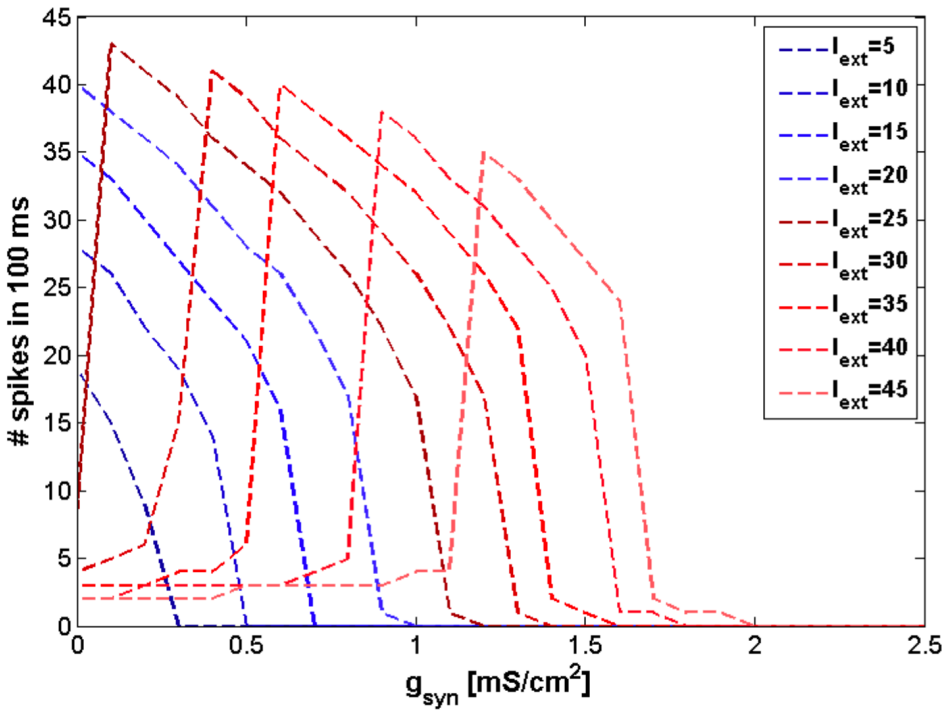

Figure 3. Deterministic case. Number of action potential generated by the postsynaptic cell in the first 100 ms of activity as a function of g_{syn} and for different values of I_{ext}. Blue lines show the result of increasing $\bar{g}_{syn}$ for $I_{ext} \leq 20 \frac{\mu A}{cm^2}$ and red lines for $I_{ext} \geq 25 \frac{\mu A}{cm^2}$.

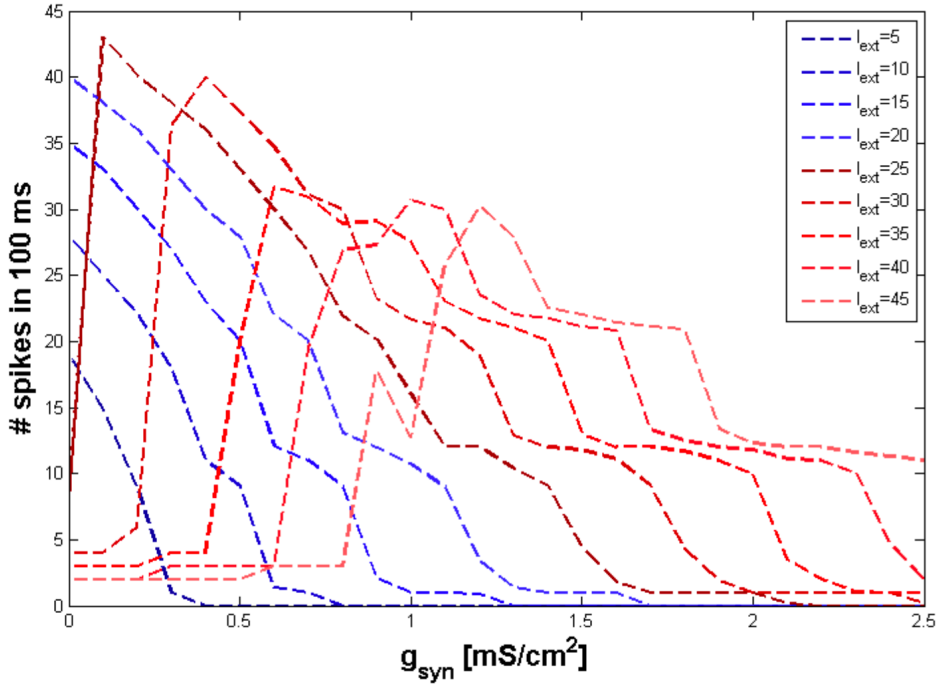

Figure 4. Stochastic case. Number of action potential generated by the postsynaptic cell in the first 100 ms of activity as a function of $\bar{g}_{syn}$ and for different values of I_{ext}. Blue lines show the result of increasing $\bar{g}_{syn}$ for $I_{ext} \leq 20 \frac{\mu A}{cm^2}$ and red lines for $I_{ext} \geq 25 \frac{\mu A}{cm^2}$.

Next, we analyzed how a GABAa-mediated inhibitory synaptic current influences the neuronal activity for different values of the depolarizing applied current. In particular, we took into account the variation on the number of action potentials generated in the postsynaptic cell as a function the synaptic conductance $\bar{g}_{syn}$. Note that this parameter represents the strength of the synaptic connection. For the deterministic model of the synaptic current, results are summarized in Figure 3 and for the stochastic model of in Figure 4.

In this figures, the number of action potentials generated in the postsynaptic interneuron are plotted versus the maximal synaptic conductance, for different values of I_{ext}. Here, we highlight two interesting facts. First of all, even though quantitatively speaking some critical values are different (for instance the peak number of spike for a given value of I_{ext} or the value of $\bar{g}_{syn}$ for which the postsynaptic cell is silent), in both models the qualitative behavior of the graphics are consistent.

In fact, in both cases, for $I_{ext} = 5 \frac{\mu A}{cm^2}$ the activity of the cell progressively decreases when $\bar{g}_{syn}$ increases. This means that strengthening the synaptic connection causes an increasing inhibition on the

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postsynaptic cell, as expected. The same occurs for $I_{ext} = 10\frac{\mu A}{cm^2}, 15\frac{\mu A}{cm^2}, 20\frac{\mu A}{cm^2}$ (blue lines in Figure 3 and Figure 4), even though the initial number of action potentials is larger because of the stronger excitation. What is remarkable is that, for $I_{ext} \geq 25\frac{\mu A}{cm^2}$ (i.e. when the depolarization block has been triggered), increasing $\bar{g}_{syn}$ has initially the effect of exciting the postsynaptic cell (red lines). This is rather surprising as it means that, when combined with a depolarization block, the effect of a inhibitory GABAa-mediated synaptic current can be excitatory. From a dynamical system point of view this is explicable by the fact that the spiking-silent transition occurs via a supercritical Andronov-Hopf bifurcation which implies that around the bifurcation value the neuron acts as a resonator[1]. This is supposed to be a general property that characterizes all depolarization block occurring via such a bifurcation.

Finally, after a certain threshold, the effect is inhibitory again.

Discussion

The depolarization block plays an important role in the regulation of neuronal activity when CA1 pyramidal cell of the hippocampus receives an excessive amount of excitatory inputs (e.g. in case of epilepsy). In this work we sought the presence of depolarization block in an exemplary model of hippocampal interneuron.

We found that our model exhibits a depolarization block for a value of the input applied current consistent with previous findings. In fact, a membrane surface of 1250~μm^2 (as in [4]) corresponds to a depolarization block occurring for $I_{ext} \approx 314\,pA$, which is in the physiological range observed in CA1 pyramidal cells by D. Bianchi et al. ([12]).

This means that this phenomenon should be taken into account when one considers models of biological neural networks in which interneurons are considered. In fact this can create a malfunctioning of the memory formation process which could be related to memory diseases, such as Alzheimer disease.

In addition, adding a single synaptic inhibitory current, we where able to study the effect of the modification of the parameter $\bar{g}_{syn}$ in the cases of two different forms of this current. This is particularly interesting because $\bar{g}_{syn}$ is the parameter which is modified when effects of synaptic plasticity are taken into account. Synaptic plasticity is known to take place when glutamatergic synapses are frequently (or rarely) stimulated, by adding (or removing) AMPA receptors, which results in an increasing (or decreasing) of the maximal synaptic conductance. At the same time, in the last decades ([13]) the

analogous process of synaptic plasticity occurring at inhibitory synapses has represented a fast developing research topic. This suggests the need for computational studies of this phenomenon.

Finally, we showed that if the maximal synaptic conductance is not too large, an inhibitory GABAa-mediated synaptic current can have excitatory effects if affecting a silent neuron
insensible to excitatory signals due to a depolarization block.

Footnotes

[1] A resonator is a neuron exhibiting subthreshold oscillations. For further information see [11]

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Declarations

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