Modulation of carbachol-evoked gamma activity in vitro with low-amplitude AC electric fields

Davide Reato, Marom Bikson and Lucas C. Parra

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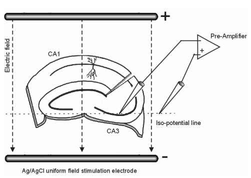
Department of Biomedical Engineering, City College of the City University of New York, New York, NY, U.S.A.

Introduction

Oscillations of field potentials at gamma frequencies (30-80 Hz) are normally present in the brain. Applied oscillatory electric fields that are comparable in magnitude to endogenous fields have been shown to affect the ongoing gamma rhythms (Deans 2007). We characterize the effects of low amplitude electric fields on carbachol induced gamma activity in rat hippocampal slices and explain the effects with a computational network model. The results are used to make predictions on the role of endogenous fields (feedback) and the effects of low amplitude electrical therapies used to threat brain disease.

Methods

***In vitro* experiments**: horizontal hippocampal slices (450 micrometers thick) of male Wistar rats (3 weeks) were used. Slices were superfused in an interface recording chamber at 34°C and oxygenated (with 95% O_2, 5% CO_2) with artificial cerebrospinal fluid (ACSF) consisting of (in mM): NaCl, 126; KCl, 3; NaH_2PO_4, 1.25; $MgSO_4$, 2; $CaCl_2$, 2; $NaHCO_3$, 24; glucose, 10.



Gamma oscillations were induced using 20 µM of carbachol (Fisahn 1998, Traub 1996). Recordings of extracellular field potentials in hippocampus (CA3) were obtained using glass micropipettes (2-6 MΩ) filled with ACSF. The data were low-pass filtered at 100 Hz and digitized at 2 kHz.

Sinusoidal spatially-uniform electric fields were applied to slices with varying frequencies and amplitudes. Stimulation artifacts were minimized by measuring relative to an iso-potential electrode and with successive digital subtraction. Spectral analysis was performed using short-time (300 ms) Fourier transform.

Even if the carbachol model is not totally physiological (the induced oscillations persist for hours) it is of a good representation of the gamma activity projected to the brain slices model.

Computational model: the modeling of the neuronal network was implemented adapting Izhikevich's model (2003) to describe the dynamics of 800 hundreds of pyramidal neurons and 200 inhibitory neurons.

The equations describing the electric behavior of a single neuron are:

$$\dot{v} = 0.04v^2 + 5v + 140 - u + I$$

$$\dot{u} = a(bv - u)$$

$$\text{if } v \geq 30 \text{ mV} \rightarrow \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases}$$

where the parameters for pyramidal (Py) and inhibitory (In) neurons are the same than those reported in Izhikevich (2003).

The synaptic strengths depend on the type of connection (Py-Py, Py-In, In-Py, In-In) and all the synaptic currents were low-pass filtered to reflect the time constant of neuronal membrane. The presence of carbachol was simulated as a membrane depolarization of pyramidal neurons.

The effect of the electric field applied was considered as an input current for pyramidal neurons so that the total current for each neuron is the sum of the synaptic inputs, the polarization current for the electric field and a noise term.

$$I = \sum_{\text{AP fired}} I_{syn} + I_{pol} + I_{noise}$$

References

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Bazhenov M., Rulkov N. F., Timofeev I. (2008), J Neurophysiol. 100(3):1562-75

Berzhanskaya J, Gorchetchnikov A, Schiff SJ. (2007), Neurocomputing. 2007 Jun;70(10-12):2091-2095

Deans JK, Powell AD, Jefferys JG (2007), Sensitivity of coherent oscillations in rat hippocampus to AC electric fields

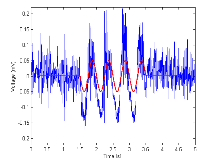
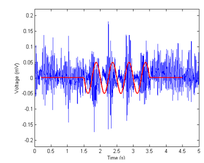
Traub RD, Whittington MA, Colling SB, Buzsáki G, Jefferys JG (1996), J Physiol. 1996 Jun 1;493 (Pt 2):471-84

Results

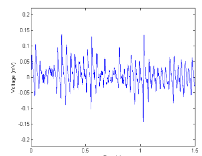
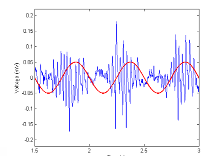
In general, increasing the amplitude of the stimulation increases the strength of the following observed phenomena. The minimum field strength required is in reported in parenthesis.

- **Suppression but not enhancement** (3 mV/mm): DC stimulation induce suppression of gamma activity if the stimulus is hyperpolarizing but not an enhancement during a depolarizing stimulus (figures 1a,1b)
- **Modulation** (0.5 mV/mm): Low frequency stimulation modulates gamma activity (Fig 1c)
- **Subharmonics** (3 mV/mm): Stimulation between 14 Hz and 50 Hz induce population spikes at half of the frequency of the stimulation (subharmonics, Fig 1d)
- **Post-stimulus suppression**: at the end of stimulation, if subharmonics are present, there is a suppression (about 200 ms) of gamma activity (Fig 1d, oval)
- **Transient phenomena** (2 mV/mm): at the onset and offset of DC stimulation there are population spike or suppression (depending on the hyperpolarizing/depolarizing effect of the field, Fig 1a,1b)

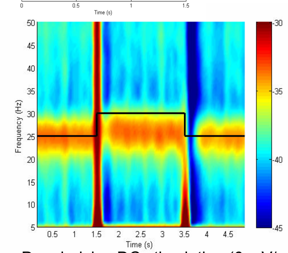
In vitro experiments

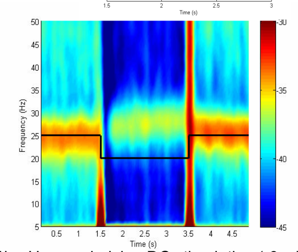
Example of AC electrical stimulation (2 Hz) before (left) and after (right) the removal of the artifact

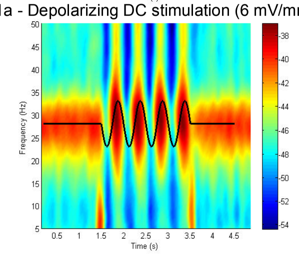
Example of gamma oscillations without stimulation (left) and during AC (2 Hz) stimulation (right)



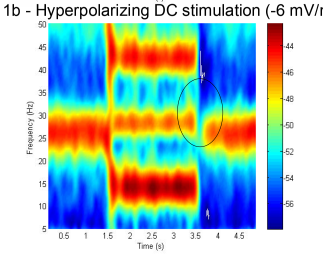
1a - Depolarizing DC stimulation (6 mV/mm)



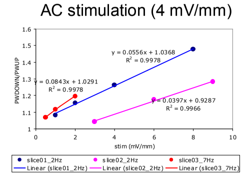
1b - Hyperpolarizing DC stimulation (-6 mV/mm)



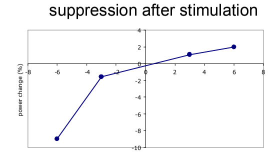
1c - Modulation of gamma activity with 2 Hz AC stimulation (4 mV/mm)



1d - Subharmonics at 14 Hz during AC stimulation at 28 Hz (6 mV/mm) and suppression after stimulation

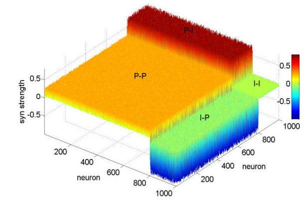


Change in the modulation strength with different amplitudes

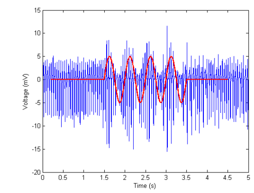


Change in the power during DC stimulation with different amplitudes

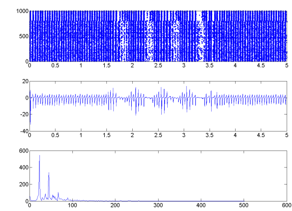
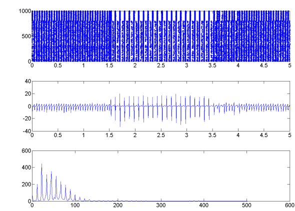
Computational model



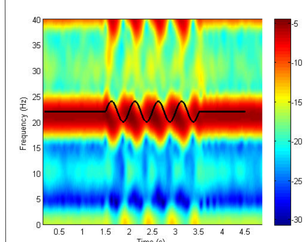
Synaptic connections used in the network model of pyramidal neurons and interneurons



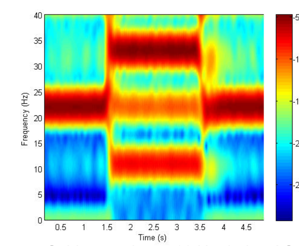
Example of 2 Hz stimulation of gamma oscillations in the network model

Examples of the results of the model. Raster plot, extracellular trace and power spectrum for (2a) 2 Hz (left) and (2b) 23 Hz the frequency of the oscillations, right) stimulation. In the first case the effect of the stimulation is the modulation of the endogenous activity, in the second subharmonics generation



Modulation of gamma activity with 2 Hz AC stimulation in the network model



Subharmonics at 12 Hz during AC stimulation at 23 Hz in the network model

Discussion

Weak electric fields, which cause only a small polarization of the somatic membrane, none-the-less have profound effects on coherent gamma activity. Several mechanisms underlie the sensitivity of gamma oscillation to electric fields; that are, in part, waveform specific. The general sensitivity of gamma oscillation to electric fields results from:

- neurons remaining close to AP threshold
- coherent polarization of a network
- neuronal coupling enhancing sensitivity
- related compensation and recovery mechanisms.

Modulation is mediated by a change in network firing rate (Fig 2a). Sub-harmonics are mediated by an increased precision of pyramidal firing, which in turn, results in a more robust inhibitory volley (Fig 2b). Despite linear membrane polarization of isolated single neurons, DC responses are non-linear and demonstrate compensation, both reflecting network response.

davide.reato@gmail.com