Low-amplitude electric fields modulate the dynamics of a neuronal network oscillating at gamma frequencies

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Introduction

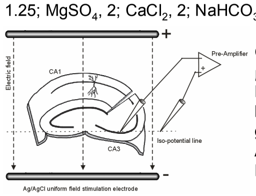
Weak electric field can modulate the dynamics of a neuronal network (Francis 2003), including in the gamma band (Deans 2007, Berzhanskaya 2007).

Ictal phenomena may be preceded by an increase in the gamma band power in EEG signal. In the present study, we modulated carbachol-induced gamma activity in brain slices using low-amplitude (<10 mV/mm) DC and AC electric fields. The experimental results were reproduced in a computational neuronal network. We considered, in particular, how the effects of the electric field on single neurons influence the dynamics of the whole network.

The implementation of a simplified network model allowed a mechanicistic understanding of the effect of an electric field on network activity.
The results reinforce the importance of network state in determining the response to electrical stimulation.

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). Artificial cerebrospinal fluid (ACSF) consisted 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 (Gluckman 1996) and with successive digital subtraction. Spectral analysis was performed using short-time (300 ms) Fourier transform.

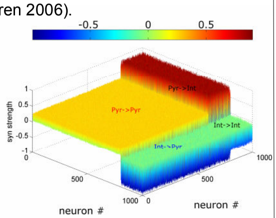
Computational model: The modeling of the neuronal network was implemented adapting Izhikevich's model (2003) to describe the dynamics of 800 hundreds pyramidal neurons and 200 inhibitory neurons.

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

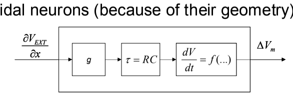
$$\dot{v} = 0.04v^2 + 5v + 140 - u + I$$
$$\dot{u} = a(bv - u)$$
$$\text{if } v \geq 30 \text{ mV} \rightarrow \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases}$$

The parameters used for pyramidal (Py) and inhibitory (In) neurons were chosen representative of physiological behaviors (Oren 2006).

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 the synaptic connections. The presence of carbachol was simulated as a membrane depolarization of pyramidal neurons only (Fisahn 2002, Bartos 2007).



The effect of the electric field applied was modeled as an RC circuit with a coupling constant (g) chosen from previous literature. The field was assumed to affect only pyramidal neurons (because of their geometry).



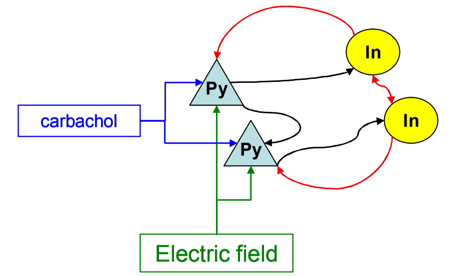
The total current for each neuron is the sum of the synaptic inputs, the polarization current for the electric field and a noise term.

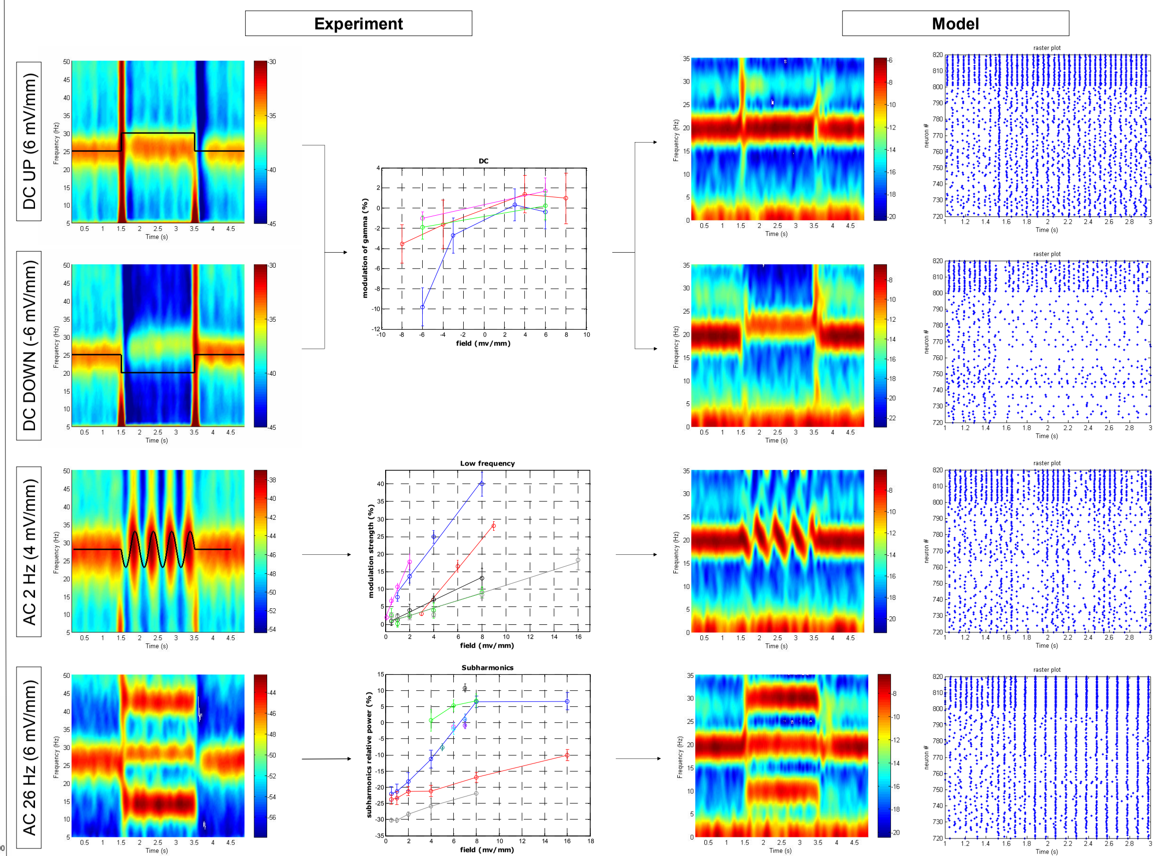
$$I = \sum_{\text{AP fired}} I_{syn} + I_{pol} + I_{noise}$$

Results

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

- **Suppression but not enhancement** (3 mV/mm): DC stimulation induces suppression of gamma activity if the stimulus is hyperpolarizing ("DC DOWN") but not an enhancement during a depolarizing stimulus ("DC UP")
- **Modulation** (0.5 mV/mm): Low frequency stimulation modulates (in amplitude) gamma activity
- **Subharmonics** (5-6 mV/mm): Stimulations between 20 Hz and 40 Hz induce small population spikes at half of the frequency of the stimulation (subharmonics)
- **Post-stimulus suppression**: at the end of the stimulation, if subharmonics are present, there is a suppression (about 200 ms) of gamma activity
- **Transient phenomena** (2 mV/mm): at the onset and offset of DC stimulation there are population spike or suppression of gamma activity (depending on the hyperpolarizing/depolarizing effect of the field)





Depolarizing DC stimulation induces a small increase of the firing rate of pyramidal neurons.

Hyperpolarizing DC stimulation induces a decrease in the firing rate of pyramidal neurons. That reduces the power of the oscillations.

Low frequency stimulation induces modulation of the firing rate of pyramidal neurons and so of the power of the oscillations

Electric fields with frequencies between **~20 and 40 Hz** generate subharmonics. This is because the firing of pyramidal neurons become more precise.

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
- neuronal coupling enhancing sensitivity
- coherent polarization of a network
- related compensation and recovery mechanisms

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

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