Electrical Stimulation in Neuronal Cultures Alters Burst Initiation And Reveals Strong Network Remodelling

A. C. Haeb[1,2,3], **M. Ocio-Moliner**[1,2], A. M. Houben[1,2], J. Soriano[1,2]

[1] Departament de Física de la Matèria Condensada, Universitat de Barcelona, E-08028 Barcelona

[2] Universitat de Barcelona Institute of Complex Systems (UBICS), E-08028 Barcelona

[3] Departament de Biomedicina, Institut de Neurociències, Universitat de Barcelona, E-08036 Barcelona

A crucial feature of neuronal cultures is their capacity to spontaneously activate in a quasi-synchronous manner (*network bursts*). On the other hand, electrical stimulation, delivered through microelectrode arrays (MEAs), has proven not only able to elicit bursts but also to modify spontaneous activity by reshaping functional connectivity [1]. However, the mechanisms underlying bursts generation and their relationship with synaptic plasticity remain elusive.

In this study, we employed a high-density MEA with a physiologically plausible stimulation protocol, combining tetanic and low frequency stimulation [2], to induce long-term potentiation in dissociated *in vitro* cultures. The analysis of neuronal activity before and after stimulation revealed a displacement of the foci of burst initiation towards apparently random locations, i.e. apparently unrelated to the stimulated electrodes. However, this change was observed only in certain spatial configurations of the stimulated electrodes, suggesting that burst initiation is not governed solely by local interactions [3].

To analyse the impact on network connectivity, we used transfer entropy to quantify the change in the connection weights of functionally linked neurons. Our findings show a reduction in the post-stimulation average weights as well as the emergence of a few stronger interactions within the network. In addition, we observed a correlation between the migration of burst initiation points and connection strengthening among localized groups of neurons, indicative of network reorganization.

Overall, our study represents a first step towards deciphering the interplay between plasticity and spontaneous activity in *in vitro* neuronal networks.

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