One-dimensional Neural Cultures Support Propagating Activity with Variable Amplitude and Velocity

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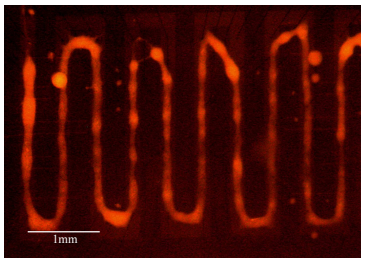
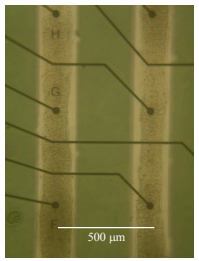
Abstract

We find that neural activity with variable amplitudes can propagate over long distances in one-dimensional cultures of rat hippocampal neurons. The activity is measured by either Multi-Electrode Arrays or by Calcium fluorescence imaging. Variability of an order of magnitude in both propagation velocity and firing rate amplitudes of spontaneous activity fronts is detected, with a linear relation between velocity and amplitude. Initiation of waves can occur spontaneously or by electrical or chemical stimulation, with different resulting velocities and amplitudes. These results current models for signal propagation in neural media, including synfire chain models, is discussed in the light of these new results.

Methods

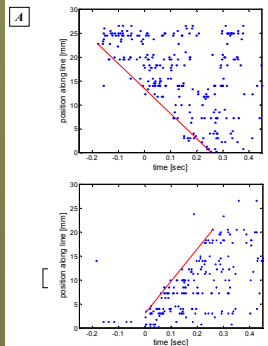
We grow rat hippocampal neurons in a linear culture which is aligned on a multi-electrode array. Up to 120 neurons are recorded from. Extracellular potentials from up to 60 electrodes are amplified x1000, low-pass filtered at 3KHz and sampled in 18KHz. Single neuronal spikes are detected by a deviation of at least 15μV and 3 standard deviations of the measured voltage from the baseline. Propagating fronts emerge spontaneously or by stimulation of the culture.



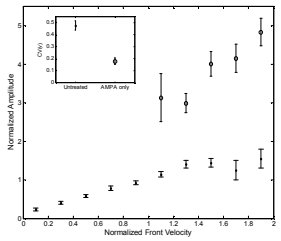


One-dimensional rat hippocampal cultures (n = 11) that are 70 - 144 μm wide and 10-45 mm long, and include including 2000 - 12000 cells, were grown on multi-electrode arrays. Depending on culture length, we monitored the activity of 50 - 150 neurons that are 1.5 - 4% of the neurons in the culture.

Spontaneously Generated Fronts



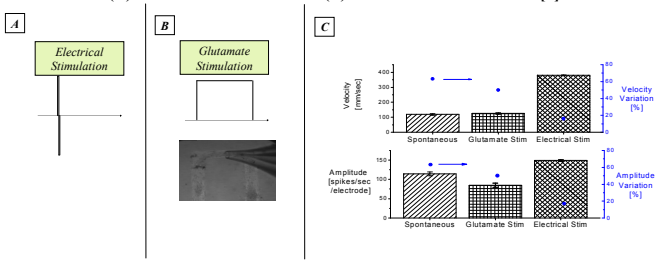
Spontaneously generated fronts propagate along the culture (A), presenting firing amplitude which varies between different bursts. (B) Generation of fronts may take place at preferred initiation positions.



Amplitude as a function of Velocity of spontaneously generated fronts in untreated (stars) and $GABA_A$ and NMDA-blocked cultures. The variation diminishes with the disinhibition (inset).

Stimulation of the Culture

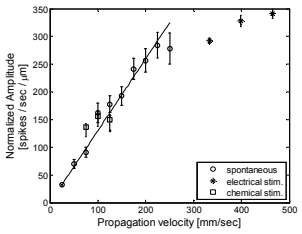
We stimulate the culture locally to elicit propagating fronts [1], using (A) Electrical stimulation and (B) local chemical stimulation [2]

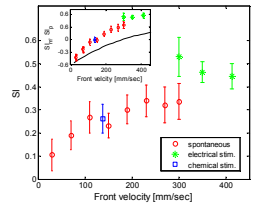


By eliciting the culture using different methods we drive fronts of different propagation velocities and amplitudes. (A) Focal electrical stimulation, using a 500 μs, 280-570mV bipolar pulse, is achieved using one of the embedded electrodes. (B) Focal chemical stimulation using concentric dual pipette [2] loaded with 100μM of glutamate, and applied in 100 msec puffs. (C) Comparison of propagation velocity and amplitudes that result from spontaneously generated, electrically evoked and chemically (glutamate) evoked fronts. The Spontaneously generated as well as chemically generated fronts have similar average velocities, while the electrically stimulated fronts have x3 higher velocities. Results are similar for the amplitudes.

Velocity of Fronts correlates with Amplitude and Synchrony

We characterize each propagating front by two quantities, firing rate amplitude and synchrony. We measure a correlation of the front velocity with the firing rate, and see that the chemically stimulated fronts lie on the amplitude-velocity curve of spontaneous activity. Electrically evoked activity deviates from this curve, showing a saturation in the firing rate amplitude. The higher velocities measured for fronts with similar may be attributed to a higher degree of synchrony that we measure in electrically evoked activity.





The variability observed in velocities, which is spans an order of magnitude, is correlated to the firing amplitude.

Firing amplitude is defined as the firing rate within [-10,20] msec of the front arrival time, averaged over electrodes in the front's propagation path.

Measured Synchrony Index

$$SI = SI_m - SI_p$$

$$SI_m = \left[\frac{E_S - E_R}{E_S + E_R}\right]_{measured} \quad ; \quad SI_p = \left[\frac{E_S - E_R}{E_S + E_R}\right]_{predicted}$$

Where

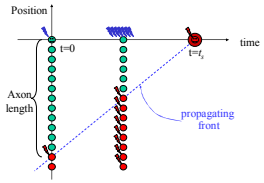
E_S *is the fraction of participating electrodes which fire within tsyn=3msec after the front arrival*

E_R *is the fraction of all other participating electrodes*

An electrode participates in a front if it fires once or more within 20msec after front arrival.

Model

We use a simple model to explain the relation between the firing rate amplitude and the propagation velocity of a front, along the lines of [3] with addition of a firing rate. The model explains the amplitude-velocity relation we measure along with a prediction for the range of firing rates in which the relation is maintained.



We assume that neurons behind the propagating front fire at a constant rate R. , and consider a postsynaptic neuron, which starts receiving inputs from the front as it arrives at a distance σ from the neuron. The neuron will fire at time t_s.

We take

- *σ the mean axonal length.*
- *N the number of neurons within σ.*
- *g_s synaptic strength*
- *V_T firing threshold potential*

And define

- *c the front propagation velocity,*

$$c = \sigma / t_s$$

Assuming that somatic EPSP integration is efficient in the time range

$$\tau_r << t_s << \tau_m$$

Time to fire is given by

$$V_T = \tfrac{1}{2} g_s N R t_s \quad \Rightarrow \quad t_s = \frac{2V_T}{g_s NR}$$

This constitutes a relation between propagation velocity and firing rate amplitude:

$$R = \frac{2V_T}{\sigma N g_s} c$$

Discussion

We measure fronts which propagate at a propagation velocity that is correlated with its amplitude and synchrony. The velocities show large variation about their mean (CV~0.5-1) and consequently span about an order of magnitude. These characteristics seem to be set at the initiation of the front, and are kept along its propagation.

Our results stand in agreement with rate transmission models [3], as we see that partly-synchronized fronts propagate and maintain rate along the culture, presumably because of recurrent connectivity [4]. Still, as predicted by synfire chain models, highly synchronized front indeed propagate faster, while maintaining synchrony [4,5].

Conclusions

- **We measure propagation of fronts in uni-dimensional (linear) rat hippocampal cultures using Multi-electrode arrays. These cultures restrict propagation to a single path, thus forcing causality in neural activation. The fronts propagate over long distances (>30 synaptic hops) while maintaining their velocity and firing rate amplitudes.**
- **Spontaneously generated fronts show high variability above an order of magnitude in both their propagation velocities and firing rate amplitudes. For example, propagation velocities span a range of about 20 - 270 mm/sec.**
- **Chemically evoked fronts propagate in velocities similar to the spontaneously generated ones but with reduced variability. Electrical stimulation, on the other hand, renders highly synchronized fronts which also propagate faster than the spontaneous ones.**
- **Initial conditions seem to set front characteristics. A simple model is devised to explain the amplitude-velocity relation observed for spontaneously generated fronts, given that rate is stable. Our results agree with some of the aspects of rate transmission models as well as synfire chain models.**

References

[1] Feinerman O, Segal M, Moses E, *J Neurophys*, 94(5) 3406-3416, 2005.
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[4] Litvak V, Sompolinsky H, Segev I, Abeles M, *J Neurosci*, 23, 3006-3015, 2003.
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