

## Small fields change spike timing: A functional role of local-field potentials?

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Small electric fields will polarize neurons by only a small amount; for this reason small electric fields have previously been suggested to have no physiologically relevant effects. However, in recent years evidence has been mounting that small fields can entrain network activity [1], and have indeed a causal effect on brain function [2]. To date, there is no proven mechanistic theory on how this causal interaction may occur. We propose a simple mechanism whereby an extracellular field incrementally polarizes the neuron's membrane and thus advances (or delays) the timing of a synaptically driven action potential. Assuming a steady firing threshold and knowing that a membrane polarizes in proportion to field strength [3], i.e.  $\Delta V = cE$ , one can make a number of quantitative predictions on the effects of extracellular fields on a neuron's spike timing: (1) Spike timing changes linearly with increasing steady-state field strength:  $\Delta t \propto E$ . (2) This effect is proportional to the inverse of the driving synaptic membrane potential slope:  $\Delta t = \Delta V / \dot{V} = cE / \dot{V}$ . (3) Oscillating fields will shift firing times with their mean falling within 1/4 of the oscillatory cycle (the rising edge). (4) This mean firing time advances with increasing field strength and decreasing ramp slope, i.e. it increases with  $cE / \dot{V}$ . (5) The strength of the coherence as measured by the Rayleigh coefficient (vector strength) also increases with  $cE / \dot{V}$ .

To test these predictions we measured the effect of applied uniform fields on the timing of action potentials of CA1 pyramidal cells *in vitro*. Spikes were evoked by injecting intracellular current ramps that simulated depolarizing synaptic drive in the theta range (4-8Hz) while applying steady-state fields as well as field oscillations in the gamma range (30Hz). These experiments confirmed all our predictions. Thus, we show that steady-state fields with field strength of  $E = 1\text{mV/mm}$  and synaptically driven theta ramps can advanced spiking by up to  $\Delta t = 1\text{ms}$ , while gamma fields showed synchronized spiking coherent with the applied oscillation. We note that this field strength is well within the physiological range of normal gamma activity in the hippocampus [4]. For the hippocampus we argue that an additional synchronizing effect may result during recurrent network activity as synchronous firing causes coherent local field potentials which in turn coherently polarize many cells leading to small changes in time that can add up over multiple cycles [5].

In summary, our theory explains how small fields can advance or delay spike timing and how they may affect synchronization in ongoing network activity. It provides the first experimentally verified mechanism by which small electric fields, such as those generated during normal brain activity, could have a functional role, and gives a plausible explanation for the entrainment that has been observed in response to applied fields in humans [2].

### References

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