

# **Timing and Dynamics in Cortical Networks**

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**By studying the timing and dynamics of cortical networks in vitro, we show that these networks are intrinsically able to generate accurately timed responses hundreds of milliseconds after a stimulus. The timed responses arise as a result of network dynamics. We developed a cortical network model to account for the experimental data. We show that a simple learning rule – synaptic scaling – can lead to the emergence of dynamical states that constitute a synfire chain, and produce a population clock. Our results show that timing may not require specialized mechanisms, and suggest how temporal processing may emerge in cortical networks in a self-organizing manner.**

## INTRODUCTION

The brain processes temporal information over a range of ten orders of magnitude. In the time ranges below a second there are at least two functionally distinct scales of processing: microsecond and millisecond ranges. Microsecond processing, defined here as up to a few milliseconds, is used primarily for the detection of interaural delays, and echo-location in bats. The neural basis of processing within this time range is relatively well understood (Carr & Konishi, 1990; Carr, 1993; Casseday et al, 1994; Saitoh & Suga, 1995).

Processing on the millisecond scale (tens to hundreds of milliseconds) is a fundamental part of sensory processing, most notably of speech recognition and animal vocalizations (Tallal, 1994; Shannon et al, 1995; Doupe & Kuhl, 1999; Buonomano & Karmarkar, 2002). However, even for simple tasks, such as determining whether a pair of tones are separated by 100 or 110 ms (Wright et al, 1997), little is known about the neural mechanisms underlying timing.

In order to generate a response at a precise delay after a stimulus, or to discriminate two different intervals, the nervous system must be able to process temporal information. To date, it has been hypothesized that temporal processing may rely on number of specialized mechanisms (see Discussion), including delay lines (Braintenberg, 1967; Tank & Hopfield, 1987; Bankes & Margoliash, 1993), oscillators coupled with counters/integrators (Treisman, 1963; Miall, 1989; Treisman et al, 1990), or slow synapses/currents (Fiala, 1996; Beggs, 2000).

As an initial step toward understanding the dynamics in local cortical

networks and whether these circuits can generate timed events in the range of tens to hundreds of milliseconds we examined the late responses of cortical neurons to single stimuli. We used cortical organotypic slices, which provide a useful system to analyze neural dynamics *in vitro*. While organotypic slices initially undergo synaptogenesis, the general cytoarchitecture, laminar relationships, synaptic strengths, and excitatory-inhibitory balance are preserved (Gähwiler et al, 1997; Dantzker & Callaway, 1998; Debanne et al, 1998; Klostermann & Wahle, 1999; Yamada et al, 2000).

## RESULTS & DISCUSSION

### Timed Responses in Cortical Slices

We performed whole-cell (under IR-DIC) or extracellular recordings from supragranular pyramidal neurons, while stimulating laterally in neighbouring supragranular areas. Figure 1A shows an example of an intracellular response to a single stimulus. The initial monosynaptic EPSP is followed by a second small EPSP, and a third larger EPSP. The voltage plot, obtained over 30 min, shows that the peak response is consistent across trials and is reliably elicited between 45-55 ms. Virtually all experiments from slices of more than 10 days-in-vitro (DIV) exhibited late responses. The profile and timing of the late responses, was variable from slice to slice – the peak response ranged from 10 to 340 ms. Figure 1B shows an example in which after a brief monosynaptic-EPSP the neuron exhibits little or no activity for 150 ms, followed by a series of late EPSPs

capable of generating suprathreshold responses. The resulting post-stimulus time histogram (PSTH) exhibited a peak at 200 ms. Thus, this system is capable of generating timed responses in delay that far exceed those of monosynaptic transmission.

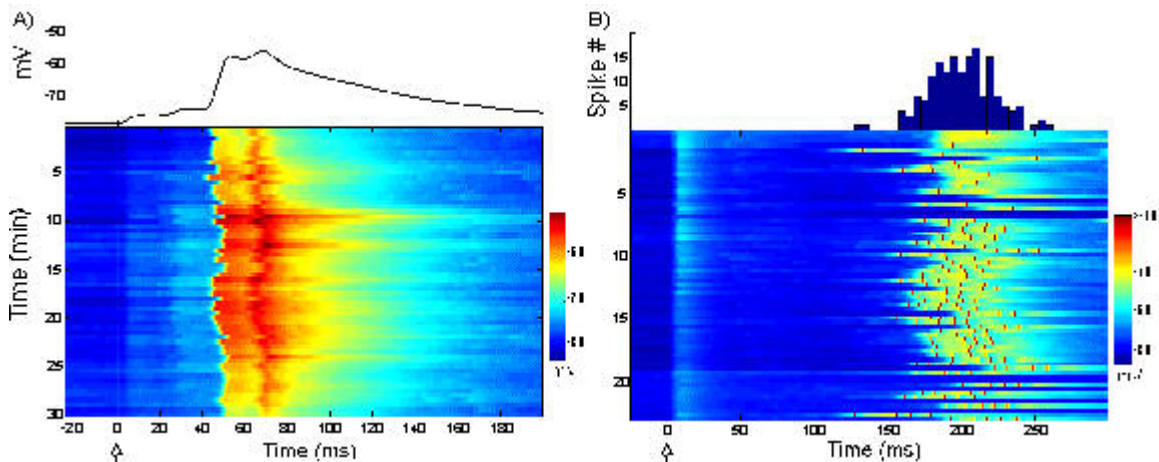


Figure 1: Timing of responses. (A) Example of timing of subthreshold EPSPs. Each horizontal sweep represents the voltage changes in response to a stimulus at time zero (arrow). A stimulus was presented every 30 sec. The trace above represents the average response over the 60 trials shown below. Note that in both the average and individual responses a small monosynaptic EPSP (mean onset of 2.7 ms), and a second small EPSP (mean onset 18.5 ms) can be observed before the large EPSP with an average onset and peak latency of 42.2 and 52.5 ms respectively. (B) Example of the timing of suprathreshold responses from a different slice. A small monosynaptic EPSP is observed at approximately 5 ms, followed by 150 ms of no apparent input, and then by a burst of excitatory input. Upper Panel. The late excitatory input often elicited spikes, which are plotted in the PSTH (time bin 5 ms).

### Polysynaptic Nature of Timed Responses

The timed responses were sensitive to the frequency of stimulation, and were abolished by high  $\text{Ca}^{2+}/\text{Mg}^{2+}$  ACSF (Berry & Pentreath, 1976), suggesting that they were generated by polysynaptic activity. Additionally, they were abolished, in an all or none fashion by APV. Together, these results suggest these networks are in a state in which excitation and inhibition are balanced to

allow a controlled propagation of activity. Specifically, excitation is not strong enough to allow runaway excitation or epileptic activity, and inhibition is not strong enough to suppress any propagation of activity throughout the network and thus the generation of polysynaptic responses. Disturbing this balance by removing the NMDA component of the excitatory drive, shifts the networks into a less active state in which polysynaptic activity was not observed.

Paired recordings revealed that different cells can respond at different time windows. Figure 6 shows an example of paired intracellular recordings from two nearby neurons (50 $\mu$ m apart). Stimulation elicited complex excitatory/inhibitory profiles in both cells, however, the spike latency was significantly different (129 vs. 205 ms). These and other experiments suggest that the timed responses are a result of the propagation of activity through functionally defined (as opposed to spatially defined) networks. In this scenario, activity propagates through functionally connected groups of neurons arranged in a feed-forward manner, e.g.,  $A \rightarrow B \rightarrow C \rightarrow \dots$ , much in the manner proposed in the 'synfire chain' hypothesis (Abeles, 1991).

### **Synaptic Scaling Leads to Synfire Chains and Population Clocks in Cortical Networks.**

To determine how these late responses might emerge in cortical networks, we performed simulations in networks composed of both excitatory and inhibitory neurons. Like the organotypic slices during the first days in vitro, the model did not exhibit any polysynaptic activity in response to stimulation in the initial state.

All excitatory synapses were plastic and followed a simple synaptic scaling rule (Leslie et al, 2001). Briefly, neurons had a target set point of activity (1 or 2 spikes per trial). The average level of activity was computed across trials, and all synapses impinging on a cell increase or decrease to achieve the target set point. Initially, since all neurons are inactive, synapses undergo a rapid increase in strength. As more and more neurons become active, some neurons will overshoot their target and synapses will be depressed.

When steady-state is achieved most excitatory and inhibitory neurons achieved their target activity level. In response to a single stimulus activity propagates within functionally defined subnetworks. Each neuron fires at a specific time window, depending on its 'position' in the chain. This network behavior corresponds to what Abeles (1991) has called a synfire chain. The maximal latency to fire within the network depends on certain variables such as number of neurons, and initial and maximal synaptic weights. In most cases the maximal latencies were around 200 ms. Thus, different groups of neurons fired at a range of different latencies from 0 – 200 ms. As a result the network implemented what we call a population clock. Time from stimulus onset can be determined by which neurons are active. Similarly, downstream neurons can fire at specific times by receiving selective inputs from a given population of neurons.

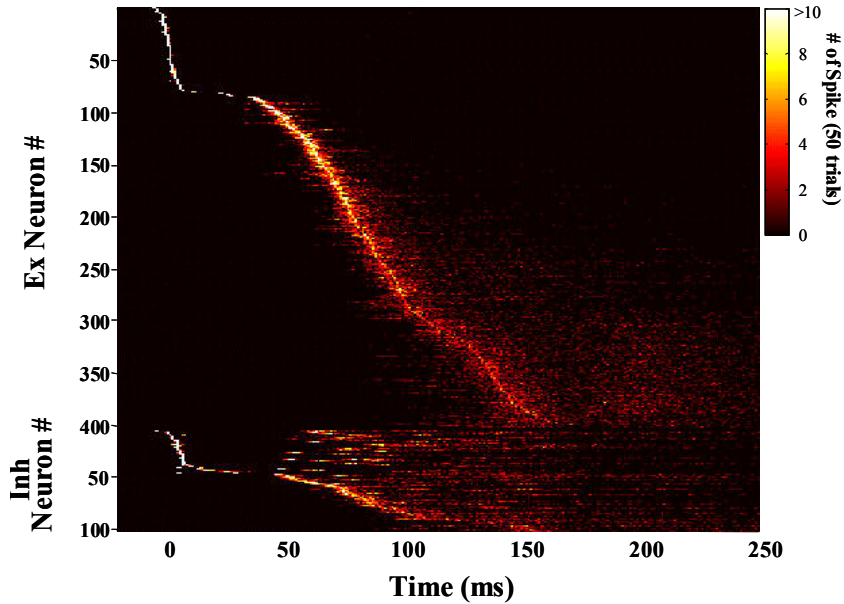


Figure 2: PSTH-Raster of network activity after training. Each line represents the PSTH of a given neuron. The neurons were sorted according to latency. Before training using a synaptic scaling learning rule there was no response to a stimulus at time 0. After training, the network organized itself into a syn-fire chain architecture. Note that in this state the network implements a population clock.

## CONCLUSIONS

Together our data show that local cortical circuits can generate reliably timed responses on the order of tens to hundreds of milliseconds. These results indicate that the balance of excitation and inhibition is carefully regulated to allow controlled propagation of activity in recurrently connected networks. Our theoretical data establishes that a simple learning rule – synaptic scaling – can account for the development of networks that exhibit controlled dynamics. Interestingly, the resulting dynamical state constitutes a synfire chain, and produces a population clock. Specifically, time from stimulus onset is encoded in the dynamically changing population vector of active neurons. This model is the first to show how temporal processing may emerge in cortical networks in a self-organizing manner. Together these results suggest that specialized timing

mechanisms such as oscillators, delay lines or some sort of 'internal clock' are not necessary. Rather, since timing is a fundamental part of sensory and motor processing, the same networks that process spatial information can concurrently process temporal information.