Spike-Timing Patterns in Cortical Neural Networks With Axonal Conduction Delays

Eugene M. Izhikevich*

January 13, 2004

In the mammalian neocortex, pyramidal neurons often project to distant regions resulting in axonal conduction delays of tens of milliseconds. Synchronous spiking of such neurons may not be effective to fire a postsynaptic cell, since the spikes might arrive to the postsynaptic cell at drastically different times. To excite the cell, the presynaptic neurons must fire with certain spike-timing patterns determined by the delays. Simulating a network of neocortical neurons with conduction delays and STDP, we found that spiking neurons spontaneously self-organized into groups and fire such repetitive spike-timing patterns with a millisecond precision. We found more groups than neurons.

The classical point of view that neurons transmit information exclusively via modulations of their mean firing rates (1) seems to be at odds with the growing empirical evidence that neurons can generate spike-timing patterns with millisecond temporal precision *in vivo* (2) and *in vitro* (3). The patterns can be found in the firing sequences of single neurons (4, 5) or in the relative timing of spikes of multiple neurons (6) forming a functional *neuronal group* (7). Activation of such a neuronal group can be triggered by stimuli or behavioral events (8). These findings have been widely used to support the hypothesis of "temporal coding" in the brain (9, 10): The synaptic input from multiple neurons converging onto a given postsynaptic neuron is much stronger when they fire synchronously. An implicit assumption here is that the axonal conduction delays are negligible.

The average axonal conduction velocity of myelinated fibers in mammalian neocortex was measured to be around 1 m/s (11), implying that it may take more than 10 ms for an action potential to travel to a postsynaptic target 10 mm away. Most of the recorded cortico-cortical and cortico-thalamic delays were in the range from 0.1 ms to 30 ms (12). Apparently, the synchronous mode of firing of presynaptic neurons is not effective to fire a given postsynaptic cell because the presynaptic spikes may arrive at the postsynaptic target at drastically different times.

For example, neuron a in Fig. 1A receives inputs from neurons b, c, and d with different conduction delays. Synchronous firing, as in Fig. 1B, is not effective to excite a. To maximize the postsynaptic response in a, the presynaptic neurons should fire with the pattern determined by the delays and depicted in Fig. 1C so that the spikes arrive at a simultaneously. A different spike-timing pattern, as in Fig. 1D, excites neuron e.

When synapses are relatively strong, the firing of neuron a in Fig. 1C is time-locked to the firings of neurons b, c, and d: It fires 10 ± 1 ms after neuron d, where the spike jitter is mainly due to the variable postsynaptic spike latency. If neurons in Fig. 1A are part of a larger network, spike-timing pattern in Fig. 1C may result in simultaneous synaptic inputs converging to other postsynaptic targets thereby eliciting time-locked response in those targets as well. As a result, the pattern in Fig. 1C may elicit spike-timing patterns in a larger population of neurons, forming a neuronal group.

One such neuronal group and its spike-timing pattern is depicted in Fig. 1E. Firing of neurons 2, 5, and 9 in the order shown in the figure results in the propagation of time-locked activity throughout the rest of the group. Here, each open box denotes the predicted spike timing of a neuron based on the spike timings of its presynaptic neurons and the conduction delays.

*The Neurosciences Institute, 10640 John Jay Hopkins Drive, San Diego, CA, 92121

It might seem that the existence of such neuronal groups is highly unlikely, since the groups require fine-tuned synaptic weights and matching (or converging) conduction delays. On the other hand, combinatorial considerations suggest that such groups can in principle be found in randomly connected networks with a distribution of conduction delays. Based on recent theoretical findings (13), we hypothesized that spike-timing dependent plasticity (STDP, 14) can select matching conduction delays and spontaneously organize neurons into such neuronal groups.

To test this hypothesis, we simulated a model (15) having 1000 spiking neurons and 100,000 synaptic connections with STDP and random conduction delays in the range from 1 ms to 10 ms. The model has 800 excitatory neurons of the regular spiking type and 200 inhibitory neurons of the fast spiking type (16). The initial values of synaptic weights were random, and STDP quickly evolved the network into an asynchronous state with balanced excitation and inhibition (17) and mean firing rate of 2 Hz for excitatory neurons and 15 Hz for inhibitory neurons.

The standard procedure to determine spike-timing patterns *in vivo* relies on statistical analyses of spike rasters (2). Instead, we developed an algorithm (18) that analyzes excitatory synaptic weights and conduction delays and finds all matching connectivity patterns, such as the one in Fig. 1E, which forms the anatomical basis of a neuronal group. In this figure, each box denotes the predicted spike timing of the neuron based on the spike timings of its presynaptic neurons and the conduction delays. Once the predicted spike-timing pattern is found, we can use it as a template to scan the spike raster to find when the group was activated, i.e., its constituent neurons fired with the predicted pattern and ± 1 ms spike jitter. Two such examples are shown in Fig. 1F and G, which are magnifications of the spike raster in Fig. 1H.

In Fig. 1I we start simulation with a random connectivity, and determine the number of different neuronal groups every 1 minute. As one expects, the number initially increases and after 1 hour saturates at a dynamic equilibrium around 6,000. At time 24 hours, we shuffle the weights of all excitatory $\rightarrow$ excitatory connections without changing the conduction delays. The number of groups dropped to 470 and then slowly re-grew. Thus, majority of neuronal groups need spiking activity and STDP to appear and persist.

The distribution histogram of the size of neuronal groups at time 24 hours (before and after synaptic shuffling) is depicted in Fig. 1J. Though the majority of groups are small, there are many groups consisting of tens of neurons. At one moment, not shown in the figure, our algorithm found a group of size 800; that is, all excitatory neurons, if ordered appropriately, had matching connectivity. Such a group did not persist though.

We kept the record of the time moments each group first appears and disappears during our 24-hour simulation, and plot the distribution of the life spans (19) in Fig. 1K. More than 31,000 different groups were registered; The majority were short-lived, though 471 groups survived the entire 24-hour simulation (bin ">24"). Thus, the dynamic equilibrium in Fig. 1I consists of 471 core groups and more than 5,000 transient groups that appear and quickly disappear.

Our definition of a neuronal group relies on the anatomy of the network, and not on its dynamics. (Of course, the former and the latter are dependent via STDP.) We say that a group was 80%-activated when at least 80% of its constituent neurons fired according to the prescribed spike-timing pattern with ± 1 ms spike jitter. For example, the neuronal group in Fig. 1E was 88%-activated twice during a 10 sec period shown in Fig. 1H. In Fig. 1L we plot the distribution histogram of the averaged frequency of 80%-activation of neuronal groups taken from the ">24" bin in Fig. 1K, i.e., the groups that survived the entire 24-hour simulation. The mean activation frequency was 7 times per hour, i.e., every 8 minutes. Activation frequency in a surrogate spike raster (20) was much lower indicating that group activations, such as in Fig. 1F and G, are statistically significant.

Most theoretical studies of temporal coding in the brain concern the stability of synchronous firing propagating via pools in a synfire chain (9). The neuronal groups with spike-timing patterns that we describe here, are quite different from synfire chains in the sense that there are no pools and spiking is not synchronous. In addition, we are not concerned with the stability of such groups. Instead, we employ the population thinking (7): Even though the majority of the groups are short-lived, there is a huge number of them constantly appearing. Even though their activation is not reliable, tens of them activate every second in a network of 1000 neurons.

It is not surprising that STDP selects connections with matching delays from a broad distribution of axons with random delays (13) and leads to spontaneous formation of neuronal groups with precise spike-timing patterns. What was surprising that we found more groups than neurons and that an average neuron

could participate in 60 different neuronal groups at the same time. Since the groups are rarely activated simultaneously, the neuron can fire as a part of one group at one time and as a part of another group at another time without any confusion. We also found that 94% of all spikes of an averaged neuron are not affiliated with any found group, but are random.

Pure combinatorial considerations show that there could be quite different neuronal groups consisting of exactly the same neurons but firing with different spike-timing patterns. For example, the three neurons, 2, 5, and 9, firing with a pattern different from the one shown in the Fig. 1E are part of another neuronal group. This is possible because there is a broad distribution of axonal conduction delays. If all delays are the same, e.g., zero, as most computational neuroscientists assume, see though (10), then synchronicity is the only effective mode of spiking and the majority of spike-timing patterns cannot occur. We hypothesize that cortical spiking networks with axonal conduction delays may use relative spike timing as an additional set of variables for information processing that leads to a combinatorial explosion of the number of possible states.

Finally, we (in collaboration with N. Desai) tested the stability of such neuronal groups using iteratively constructed network *in vitro* pioneered by Alex Reyes (22). We used dynamic clamp via SIMULINK running on DSP board dSPACE in real time to construct a feed-forward network of layer 5 pyramidal neurons from rat visual cortex recorded via whole cell patch-clamp electrodes at temperature 32C. The delays between the neurons were random in the range 1 to 20 ms, and the synaptic weights were evolved according to STDP. A noisy GABA and NMDA conductances modeled by stochastic Ornstein-Uhlenbeck process (23) were injected so that the *in vitro* neuron has *in vivo* characteristics, i.e., resting potential is around -60 mV, input resistance is around 80 MΩ, membrane fluctuations have variance around 2 mV. After 20 minutes of continuos implementation, the neurons in the *in vitro* network self-organized and a neuronal group appears, which is similar to the one in Fig. 1, but has many more neurons. These "work in progress" *in vitro* experiments will be reported in detail at the meeting.

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15. The model is presented in detain in Izhikevich E.M. (2003) Simple Model of Spiking Neurons. IEEE Transactions on Neural Networks, in press. Each excitatory neuron has synaptic connections with a random set of 100 neurons. The axonal conduction delays are random, drawn from a uniform distribution on the interval $[1, 10]$ ms. Synaptic input from cell j to cell i resets the membrane potential of the ith neuron by the variable c_{ij}, whose initial values were drawn from a uniform distribution on the interval $[0, 7]$ mV. Each inhibitory neuron has 100 synaptic connections to only excitatory neurons with delay 1 ms and $c_{ij} = -4$ mV.

The excitatory synaptic weights c_{ij} were modified according to the STDP rule by Song, S., Miller, K. D., & Abbott, L. F. (2000), with $A_+ = 0.13$ mV, $A_- = 0.1$ mV, $\tau_+ = \tau_- = 20$ ms and Δ_{ij} being the difference between the time of *arrival* of a presynaptic spike from neuron j to a postsynaptic cell i, and the time the postsynaptic cell i fires. The values of c_{ij} are kept in the interval $[0, 7]$ mV by a automatic cutoff procedure.

MATLAB file that simulates the network could be provided in the Supplementary Materials.

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18. We consider only those synaptic connections whose weight is greater than 95% of the maximal weight corresponding to EPSP of 7 mV. Three such EPSPs are enough to fire a postsynaptic cell 50% of the time. For each triplet of neurons, e.g., neurons (2,5,9) in Fig. 1E, and each spike-timing pattern, e.g., (0 ms, 1 ms, 1 ms) in Fig. 1E, we find a common postsynaptic target that receives three coincident inputs with ± 1 ms jitter, i.e., neuron 7 in Fig. 1E. The timing of firing of such a neuron is the timing of the last synaptic input plus 2 ms spike latency, i.e., the time the membrane potential reaches the peak value. Now, we consider common postsynaptic targets of the four neurons, i.e., (2,5,9,7) with the spike-timing pattern (0 ms, 1 ms, 1 ms, 4 ms) and find the next neuron that receives three or more coincident inputs. We proceed until no common targets receiving coincident inputs are found. We define the length of the group as the longest path of the graph representing the group. We discard all groups of the length less than 3.

19. We mark the first time each group appears. When the group disappears for 10 consecutive minutes, it is pronounced dead. The time difference between the moment it appears the first time and the last time before the 10-minute pause is the life span of the group.

20. Our surrogate data is obtained from the spike data by inverting the time. Such a procedure does not change the mean firing rates, interspike histograms, magnitude of cross-correlations, and other meaningful statistics. In particular, this approach is free from the criticism (21) that precise firing sequences appear exclusively by chance in spike rasters with co-varying firing rates.

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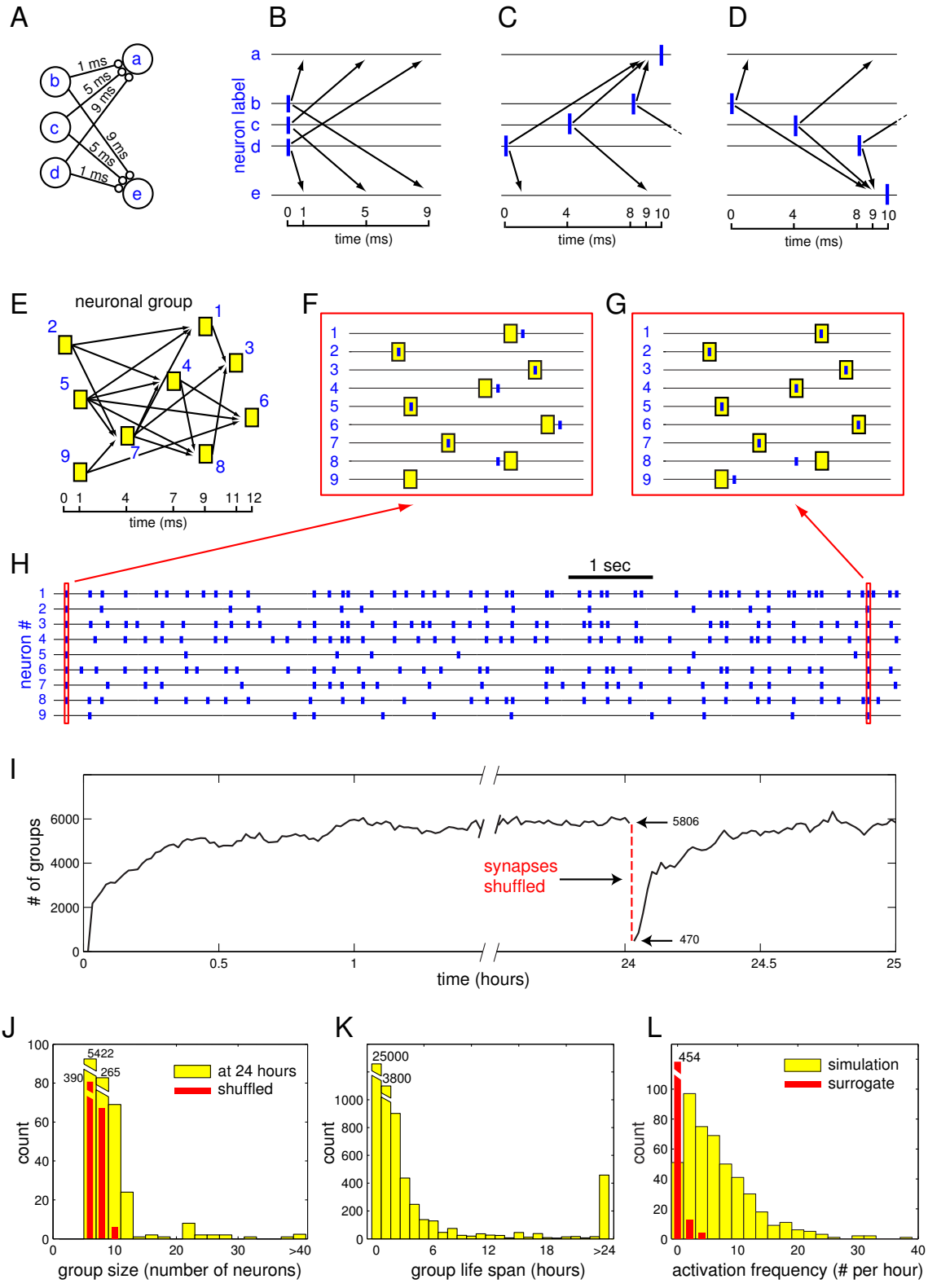
Caption to Figure 1.
(A) Synaptic connections from neurons *b, c*, and *d* to neurons *a* and *e* have different axonal conduction delays. (B, C, D) Firings of neurons are denoted by the vertical bars. Each arrow points to the spike arrival time to the postsynaptic neuron. (B) Synchronous firing is not effective to elicit a potent postsynaptic response since the spikes arrive to the postsynaptic neurons at different times. (C) The spiking pattern with neuron *d* firing at 0 ms, neuron *c* firing at 4 ms and neuron *b* firing at 8 ms is optimal to excite neuron *a* because the spikes arrive at *a* simultaneously. (D) The reverse order of firing is optimal to excite neuron *e*. (E) The pattern of connectivity and matching axonal conduction delays between neurons 1 to 9 in the simulation form an anatomical neuronal group. Yellow boxes denote the predicted spike timings of the neurons in the group. If neurons 2, 3, and 9 fire at 0 ms, 1 ms, and 1 ms, respectively, then the rest of the neurons fire in a temporal pattern marked by the boxes. (F, G) Enlargements of the spike raster (H) show reoccurrence of the predicted spike-timing pattern with ± 1 ms precision. (I) The number of different neuronal groups in the model as a function of time. At time 24 hours, the weights of all excitatory $\rightarrow$ excitatory synaptic connections were randomly shuffled. (J) The distribution histogram of the size of neuronal groups at time 24 h before (yellow) and after (red) synaptic reshuffling. (K) The distribution histogram of life spans of neuronal groups during the 24-hour simulation in (I). Total of 471 groups persisted the entire 24-hour simulation. They are in the bin marked ">24". (L) The distribution of frequency of 80%-activation of neuronal groups from the ">24" bin in (K). Red bins denote the activation frequency in the surrogate spike raster (20).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shuffled
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at 24 hours
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group life span (hours)
simulation
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activation frequency (# per hour)
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Figure 1: