Rhythmogenesis in Neurons and Networks

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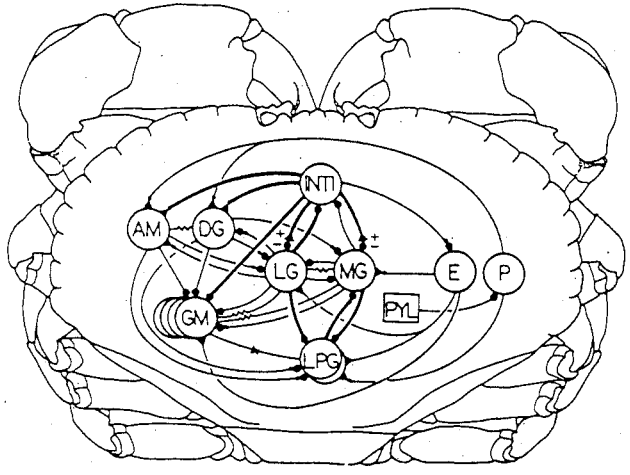

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INHIBITORY INTERNEURONS CAN SYNCHRONIZE CORTICAL PYRAMIDAL NEURONS

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Inhibitory interneurons provide a mechanism for regulating the excitation of neurons in cortical microcircuits. However, inhibition may have other functions. Computer modeling studies based on realistic simulations of cortical neurons suggest that the synapses of these inhibitory interneurons on the soma and proximal dendrites of cortical pyramidal cells are well placed for controlling the timing of impulses. Inhibitory phase-locking could occur due to the ability of inhibitory postsynaptic potentials to alter the firing rate of a cell through voltage-dependent and calcium-dependent conductances. The organization of inhibitory inputs from basket cells and chandelier cells onto a pyramidal cell might permit as few as 40 presynaptic interneurons to have as much effect on the timing of firing of a postsynaptic cell as excitatory input from 4000 presynaptic pyramidal cells.

INHIBITION IN MICROCIRCUITS

Traditionally, inhibition has been viewed as a means of turning cells off. However, in the context of a dynamic network of neurons, synaptic inputs must be viewed in terms of their effects on timing of firing rather than simply on average firing rate (Perkel et al., 1964). Inhibitory mechanisms were earlier proposed by Andersen and Sears (1968) in their "inhibitory phasing theory" to explain rhythmic firing of cells in the thalamus. They postulated that an anode break mechanism might permit thalamic cells to produce repetitive bursting due to mutual inhibitory connections. While subsequent research has caused this theory to be modified, it still appears that response to inhibition is critical in spindle generation (Steriade and Llinás, 1988). Similar inhibitory mechanisms may also occur in other brain areas. In this chapter, we will show that inhibitory interneurons

could serve to phase lock cortical pyramidal neurons (Lytton and Sejnowski, 1991).

Excitatory projections cover great distances and could provide coordinated firing between different cortical areas. Inhibitory interneurons have mainly local projections and might permit synchronization to be localized within a single column. Inhibitory interneurons could serve as control points that would allow projections from other parts of cortex to influence firing throughout a column. EPSPs can produce phase locked spiking in a quiescent cell by providing large periodic depolarizations that cause periodic spiking. Long-lasting IPSPs can do the same if a cell shows a rebound response to the level of hyperpolarization provided. Either type of postsynaptic potential can show more subtle effects in a cell that is not quiescent but shows spontaneous firing. In this case, much smaller postsynaptic potentials can shift firing times slightly and alter the firing pattern. Spontaneous background firing appears to be the rule in the central nervous system. Therefore we studied these more subtle timing effects of synaptic inputs.

Physiological experiments and neuronal modeling studies have both demonstrated that interneurons do not invariably reduce activity levels in postsynaptic neurons. In fact, an inhibitory postsynaptic potential (IPSP) can be either facilitating or defacilitating. In its facilitating role, an IPSP will increase the probability of firing in response to a following excitatory postsynaptic potential (EPSP). The facilitation may be due to de-inactivation of sodium and calcium channels or to closing of potassium channels at the hyperpolarized membrane potential. This is closely related to the phenomenon of anode break excitation, in which a burst of firing occurs following release of a neuron from an hyperpolarizing current clamp. With slightly different timing, the direct effect of IPSP hyperpolarization or conductance change will take precedence, giving defacilitation. Similarly, an EPSP can have a defacilitating effect. The defacilitation in this case could be due to inactivation of sodium and calcium channels or to activation of potassium channels during depolarization.

Phase locking of a spontaneously repetitively firing cell requires that an input be able to shift the time of firing in either direction. If a cell would otherwise fire too early, the input must delay the firing of the cell. If a cell would fire too late, the input must cause firing to occur sooner. Because postsynaptic potentials interact with intrinsic voltage-sensitive membrane conductances, an IPSP can speed up or slow down a cell's firing. Although

the speeding up is related to anode break excitation, it is a different phenomenon since it occurs in a cell that is already firing repetitively. Where an anode break response may require large sustained hyperpolarizations, inhibitory exaltation can occur with much more modest voltage transients.

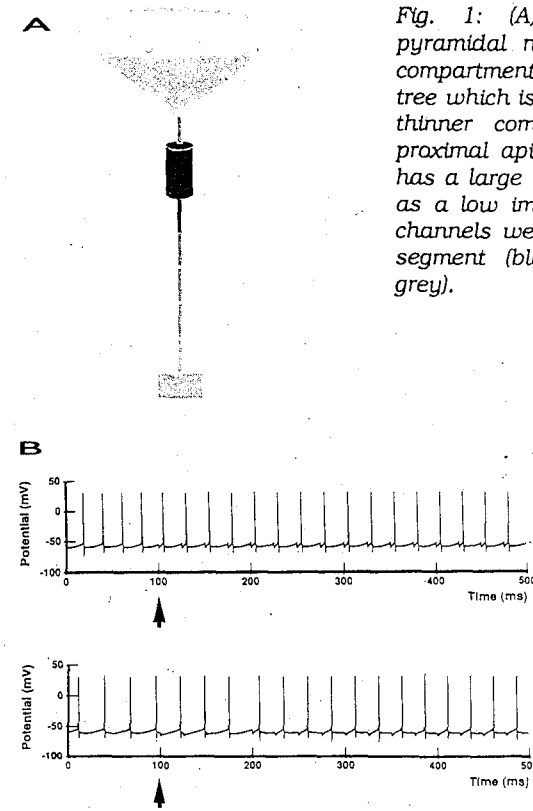

Fig. 1: (A) Compartment model of pyramidal neuron used a single large compartment to represent the dendritic tree which is connected to the soma by a thinner compartment representing the proximal apical dendrite. The axon also has a large low impedance compartment as a low impedance termination. Active channels were placed in the axon initial segment (black) and the soma (dark grey).

(B) Entrainment of the model neuron occured in response to a constant frequency 40 Hz train using hyperpolarizing conductance changes with a maximum of 60 nanosiemens (60 nS IPSPs). The IPSP train started at 100 msec (arrows). The top trace shows deceleration from 47.2 Hz to 40 Hz. The bottom trace shows acceleration of firing from 35.7 Hz to 40 Hz.

3-Channel Model Neuron

We used a simplified compartmental model of a pyramidal neuron to show how an IPSP could entrain firing to a particular frequency (Fig. 1A). The model used three voltage-sensitive channels: a fast sodium and delayed rectifier comparable to those originally described by Hodgkin and Huxley and a potassium channel with slower kinetics that permitted slow constant firing in response to excitation. The model neuron was activated

with various constant current inputs to produce regular firing from 30 to 50 Hz. After the model stabilized at the test frequency, a 40 Hz train of IPSPs was initiated in the proximal apical dendrite. The model entrained perfectly for initial frequencies between about 34 and 47 Hz (Fig. 1B). If the spontaneous cell firing was too low, inhibitory exaltation could only be maintained for a brief period. If the spontaneous rate was too high, firing frequency was irregular. The dependence of this mechanism on a limited range of firing rates illustrates that these inhibitory effects are of a modulatory nature and dependent on the initial state of the cell. This background firing, dependent on a particular balance between excitatory and inhibitory tone, could be subtly shifted by relatively small changes in the degree of synchrony between different inhibitory inputs.

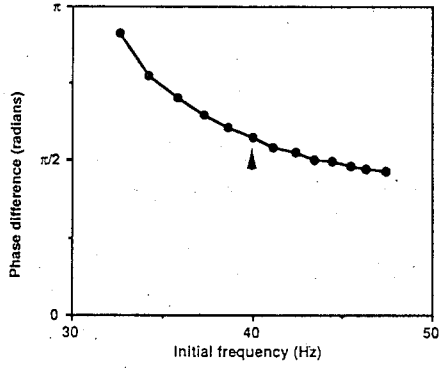

Fig. 2: The final phase difference between the IPSP and postsynaptic firing varied with the initial frequency of firing of the postsynaptic cell. Phase was measured from the beginning of the IPSP to the spike.

The phase relation between the driving inhibitory cell and the model neuron was fixed, but the value depended on the initial frequency of the model neuron (Fig. 2). At lower initial frequencies, the IPSPs accelerated firing. After the IPSP, the lag in recovery of voltage-sensitive channels causes increased inward current and early firing. The precise phase relation depends on the time course of response of these voltage-sensitive channels. As seen in figure 2, IPSPs and spikes are approximately in antiphase at these frequencies. At high initial frequencies, the IPSP inhibits firing by shunting incoming current. Therefore, the neuron fires almost immediately after the IPSP terminates. The phase lag between IPSP and spike is brief, approximately $\pi/2$.

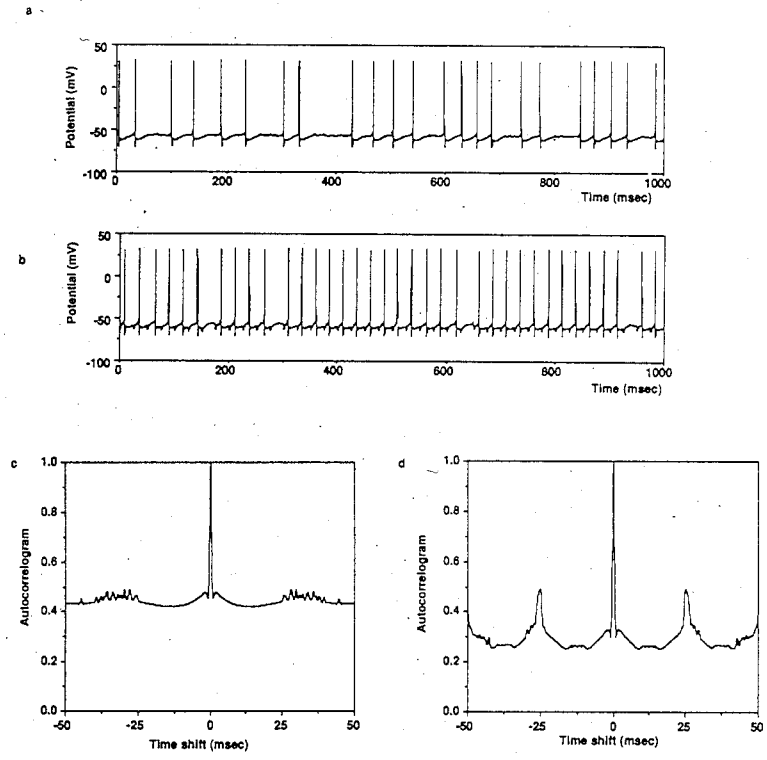

Fig. 3: Phase entrainment in the model neuron with uncorrelated multisynaptic excitation of the apical dendrite. Maximal IPSP conductance was 50 nS. (A) Slightly irregular firing is seen in the model neuron in the absence of inhibitory synaptic activity. (B) With the regular inhibitory train, entrainment of the model neuron occurs. (C) An autocorrelogram of 5 seconds of the model neuron voltage trace shown in A indicates that there is only slight correlation at 25 to 40 msec. (D) An autocorrelogram of 5 seconds of model neuron voltage trace with IPSP train (B) shows a peak at 25 msec indicating 40 Hz spike entrainment.

The previous simulations showed that IPSPs can influence neuron firing in either direction: speeding up or slowing down. We therefore simulated the effect of an IPSP train on a model neuron firing irregularly, as it might in response to sustained but uncoordinated excitation due to multiple uncorrelated synaptic inputs. The amount of excitation was tuned to produce

spiking in the 30-50 Hz range, the range for which inhibitory frequency entrainment could occur. Although the activity appeared to be fairly regular (Fig. 3A), it was uncorrelated as shown by the absence of peaks in the autocorrelogram (Fig. 3C). When the entraining IPSP was activated, the model neuron was closely entrained (Fig. 3B,D). IPSP and spikes were approximately in antiphase.

This simulation showed that phase locking of a model pyramidal cell was possible. The peak in the autocorrelogram showed the periodicity of firing. However, the phase relation of IPSP and spike was not entirely consistent. In order to get an oscillating field potential, follower pyramidal cells would have to fire simultaneously, requiring that the phase relation between driver and followers be consistent across neurons. We therefore assessed cross correlation between two model neurons sharing common IPSP input (Fig. 4). The peak at 0 msec on the crosscorrelogram indicates that both cells are firing together. The 40 Hz periodicity is evinced by the 25 msec gap between peaks. Pairwise correlations such as this in a large number of neurons would result in an oscillating population field potential.

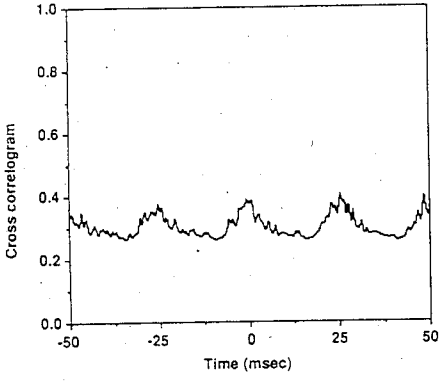

Fig. 4: A crosscorrelogram between two model neurons receiving identical trains of 50 nS IPSPs at 40 Hz shows a peak at 0 which indicates that the two cells are firing in synchrony. The next peak at 25 msec shows that they share a common frequency of 40 Hz.

There are a variety of interneuron types that could entrain pyramidal neurons through inhibitory phasing. Two interneurons that show distinct patterns of connectivity are basket cells and chandelier cells. Both interneurons typically synapse on 50 to 200 pyramidal neurons. Basket cells have axons extending up to 1 mm from their cell bodies while those of chandelier cells only extend 100 to 300 microns. Basket cells synapse

onto pyramidal cell bodies and proximal apical dendrites while chandelier cells synapse exclusively on axon initial segments. We used this latter difference to perform simulations contrasting the relative efficacy of basket cells and chandelier cells in entraining pyramidal neurons. We compared entrainment from IPSPs at the proximal apical dendrite to entrainment by IPSPs at the axon initial segment. Synapses at either location entrained the model neuron. This occurred using either shunting or inhibitory synapses and with a wide variety of parameter values including variation of specific membrane resistance, density of active channels in the soma and presence or absence of a first node of Ranvier. With all parameters, entrainment occurred slightly more easily when the IPSP was situated in the apical dendrite. The increased conductance at the spike generation zone during the chandelier cell simulation appeared to interfere slightly with the action potential preventing entrainment from very high or very low initial frequencies.

Recordings from current-clamped interneurons in cortical slices have shown that they give non-accommodating spike trains at a higher frequency than is seen with pyramidal neurons. It seemed possible that phase-locking would not occur at these high rates. Therefore, we produced IPSP trains of 200-300 Hz and assessed their effect on a regularly firing cortical pyramidal cell. We found that the model neuron spike train entrained to subharmonics of the inhibitory interneuron firing frequency. In general, the cell would find the subharmonic closest to its initial firing rate, conditioned by the amount of ongoing excitatory input it was receiving. With IPSP frequencies that are multiples of 40 Hz for example, there was a peak in the autocorrelation at 25 msec corresponding to a frequency of 40 Hz (Fig. 5). Lesser peaks in the autocorrelogram corresponded to other integral subharmonics. In figure 5, for example, there is a smaller peak seen at about 20 msec. This corresponds to a frequency of 50 Hz, another subharmonic of the 200 Hz driving frequency.

11-Channel Model Neuron

Many cortical pyramidal neurons have channels operating on widely different time scales and produce a repetitive bursting behavior (Connors and Gutnik, 1990). We were concerned that the complex interactions between the larger variety of voltage and calcium gated membrane conductances in a cortical pyramidal cell underlying the bursting behavior could interfere with the phase-locking mechanism outlined above. Therefore, we

simulated a neocortical pyramidal cell that had in its soma most of the channels that have been described in cells of this type. This included both fast and persistent sodium channels, 5 types of potassium channels including two that were calcium-sensitive, 3 types of calcium channels and a mixed channel, the anomalous rectifier. There were also several mechanisms to permit elimination of calcium. Despite the great complexity of this model, it was still relatively simple compared to a neocortical pyramidal cell with its spatial distribution of active channels in the dendrites and multiplicity of intracellular second messenger systems.

We found that the mechanism of inhibitory exaltation was also present in our more complex cell, although it was due to a somewhat different mechanism. The model would also exhibit phase locking in response to a periodic IPSP train. In order to assess how IPSP phase-locking would compare to EPSP phase-locking in this model, we designed a simulation of two pyramidal neurons, each receiving 500 very strong excitatory inputs on distal dendrites and 100 inhibitory inputs on proximal apical dendrite. These 500 excitatory inputs were meant to represent the roughly 10,000 relatively weak excitatory synapses that are found on a neocortical pyramidal cell. The locations of the synapses were chosen to correspond to the most common site of termination for these two types of projections. The two neurons started firing at different times, putting them in antiphase with respect to one another. Initially, all of the synapses onto both neurons fired randomly as individual uncorrelated Poisson processes. In separate simulations, a certain percentage of either the excitatory or inhibitory synapses were made to fire synchronously in both cells, simulating a set of shared inputs with periodic firing. With about 20 to 40 synchronization of either EPSPs or IPSPs, the two neurons shifted from firing in antiphase to firing in phase.

Although these simulations showed the efficacy of EPSP entrainment to be roughly comparable to the efficacy of IPSP entrainment expressed in percentage, consideration of absolute numbers of inputs reveals a large disparity. Since there are many more EPSP boutons than IPSP boutons on a pyramidal cell, these similar percentages indicate that many fewer synchronized inhibitory inputs produce the effect seen with a large number of synchronized excitatory inputs. As few as 40 synchronized inhibitory synapses might have as much effect as 4000 synchronized excitatory synapses. These 40 inhibitory boutons might come from as few as 5 to 10 inhibitory interneurons. The surprising efficacy of inhibitory inputs in this

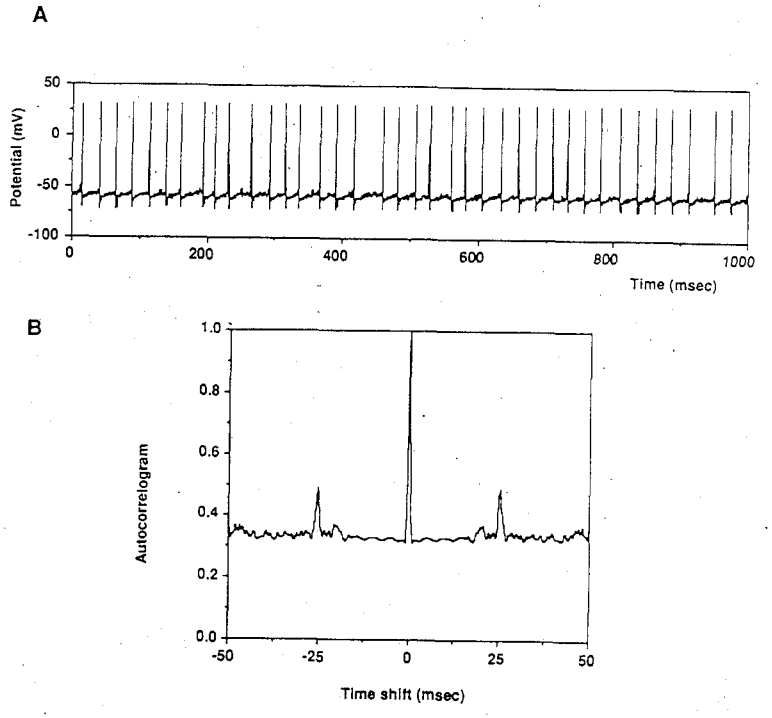

Fig. 5: Higher frequency trains of inhibitory input can also produce entrainment. In this case, a 50 nS IPSP train at 200 Hz entrains a model cell receiving uncorrelated excitatory synaptic input into the apical dendrite. The membrane potential is shown above and the autocorrelogram below. There are peaks at 25 msec and 20 msec corresponding to subharmonics of 40 and 50 Hz.

setting is probably due to two factors. First, the inhibitory inputs arise closer to the soma and spike generating zone. Therefore, they are less attenuated by passage down the dendrite. Second, in our paradigm, EPSPs must also influence a spontaneously firing cell by slightly altering the firing time on each cycle. Therefore, the EPSP must not only speed up the firing of the cell in a classical excitatory manner, but also slow down the firing at times by a paradoxical defacilitation. This defacilitation can occur due to the interaction of EPSPs and voltage-sensitive channels as noted above.

DISCUSSION

Neurons in visual cortex can be synchronized by a visual stimulus that drives the neurons in the population (Gray and Singer, 1989; Gray et al., 1989; Eckhorn et al., 1988). More surprising is the observation that neurons that are unlikely to have direct excitatory connections appear to be phase-locked; that is, fire action potentials within a few milliseconds of each other (Gray et al., 1989). Regardless of the functional significance of these correlations, their existence requires a physical explanation. In a complex, highly nonlinear system of neurons, phase-locking can occur through a variety of mechanisms (Kammen et al., 1990; Eckhorn et al., 1990; Konig and Schillen, 1991a; 1991b, Sporns et al., 1991). One particular mechanism, explored in this chapter, is entrainment and phase-locking through a common, inhibitory interneuron. Inhibition could be effective in entraining pyramidal neurons in local circuits, as we have demonstrated with computer simulations.

The significance of the correlated discharges observed in some cortical neurons remains an open question (Sejnowski, 1986). Do these synchronized neurons form a linkage that helps the later stages of visual processing group together the common elements of a coherent pattern (von der Malsburg, 1981; Wang et al., 1990)? Are the correlated patterns of firing in the ensemble of neurons actively filtering sensory information, based on the relatively small subset of neurons that are near the threshold of firing (Sejnowski, 1981)? Could synchronization be a way for the nervous system to reduce noise?

Synchronization of cortical neurons may explain some puzzling observations from area MT of monkey visual cortex. A high proportion of neurons in area MT respond selectively to the direction of motion of visual stimuli (Zeki, 1980). Moreover, in monkeys trained to detect coherent motion in randomly moving dots, the forced-choice performance of the monkey is matched by the information contained in recordings from single neurons optimally responding to the same sensory stimuli (Newsome et al. 1989). The puzzle is that the monkey does not take advantage of signal averaging over all of the relevant cortical neurons, since hundreds or thousands of neurons in the same cortical column should also respond to the same stimulus. If N neurons each with independent estimates of the same signal were averaged, the error should be reduced by $N^{-1/2}$ relative to the error from a single neuron.

Synchronization could explain the puzzle of why the information in an ensemble of neurons carrying motion signals in area MT is no better than that observed in a single neuron. Synchronization violates the assumption of independence: two neurons firing spikes at the same times carry no more information than one of them. Simultaneous recordings from several neurons in the column coding the preferred direction in area MT should therefore reveal highly correlated spike firing patterns. This resolution of the puzzle also provides an explanation for another problem. The visual stimuli used in these experiments had a high degree of noise; thus, many neurons in neighboring columns should be almost as highly stimulated as the neurons in the column with the best direction. How are the brain regions receiving projections from MT able to detect a weak signal in the presence of interference from all this activity? This is like trying to find a needle in a haystack. However, synchronization of afferents could boost the response of a neuron receiveing a projection from the synchronized population. The synchronous, converging inputs would induce a greater than the same number of uncorrelated impulses because of temporal summation in the dendritic tree of the recipient neuron. Thus, the synchronization of neurons within a column should enhance their impact on neurons in other brain regions.

One last piece of evidence for the importance of synchronous firing within a column comes from another experiment in area MT that had a remarkable result (Saltzman et al. 1990). Microstimulation of neurons in a column of neurons coding for a motion in a particular direction systematically biased the preference of the monkey for this direction of motion. Apparently, the activity of neurons in a relatively small number of neurons (perhaps as small as 100) could have a significant effect on the perceptual judgement of a monkey. It should be noted that the microstimulation should have produced synchronous activation of these neurons. Thus, the induced synchrony in the population of MT neurons could have had a large impact on other neurons receiving a projection from them by the same mechanisms suggested for neurons sychronized by the dynamics of the population.

We have demonstrated through computer simulations that converging inhibitory inputs from basket cells and chandelier cells could synchronize hundreds of pyramidal cells within a column, and that inhibition near the cell body is much more effective than synchronization through purely excitatory mechanisms within the dendritic tree. A model of a cortical

column that incorporating both inhibitory neurons and bursting pyramidal neurons exhibited a high degree of synchrony (Bush and Douglas, 1991); interestingly, the temporal pattern of the spikes in this model was not regular, as we have assumed in our study, but rather had an irregular, chaotic pattern. The firing patterns observed from recordings in visual cortex have the same character (C. Gray, personal communication). The same conclusions regarding the failure of signal averaging and the importance of temporal summation are just as valid for a chaotic time series as they are for a perfectly regular one.

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