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SIMULATIONS OF SYNAPTIC INTEGRATION IN NEOCORTICAL PYRAMIDAL CELLS

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ABSTRACT

Despite their electrotonic compactness, neocortical pyramidal cells cannot be considered as point neurons because of nonlinear interactions between inputs on the same dendritic branch. Using compartmental simulations, we have shown that dendritic saturation is significant for physiological levels of synaptic activation. We also show that the firing of about 10% of the total number of inhibitory synapses on a cortical pyramidal cell is sufficient to reduce and even completely suppress the firing of neurons receiving strong excitatory input. Finally, we present a reduced pyramidal cell model (9 compartments) that runs significantly faster yet faithfully reproduces the behavior of the full 400 compartment model. The reduced model will be used for future physiological network simulations.

15.1 DENDRITIC SATURATION

The basal and oblique dendrites of neocortical pyramidal cells are electrotonically compact [1]. A single EPSP produces virtually the same effect at the soma where ever it originates from on the basal/oblique tree. It may seem that such a neuron would resemble the point neurons used in most connectionist-type networks, but this ignores the fact that dendritic terminal segments are quite isolated from each other and have high input impedances relative to the soma [2]. These properties introduce the potential for nonlinear interactions of inputs arriving on the same dendritic branch;

the large depolarization produced in a dendrite by a single EPSP reduces the driving force on simultaneous and subsequent EPSPs on the same branch.

Ferster and Jagadeesh [3] have recently demonstrated that the size of an EPSP evoked in visual cortical cells by electrical stimulation of the LGN is reduced during depolarizations caused by visual stimulation compared to its size at the resting potential. The reduction in EPSP size was proportional to the somatic depolarization caused by the visual stimulation. Thus an EPSP that peaked at about 6mV at rest was reduced to less than 1mV when the cell was depolarized from a resting potential of -60mV to -40mV by visual stimulation (fig 9a of [3]). Ferster and Jagadeesh interpret their results as indicating that the synaptic sites (dendrites) are significantly more depolarized than the soma during synaptic activation of the cell, thus producing saturation by the process described above.

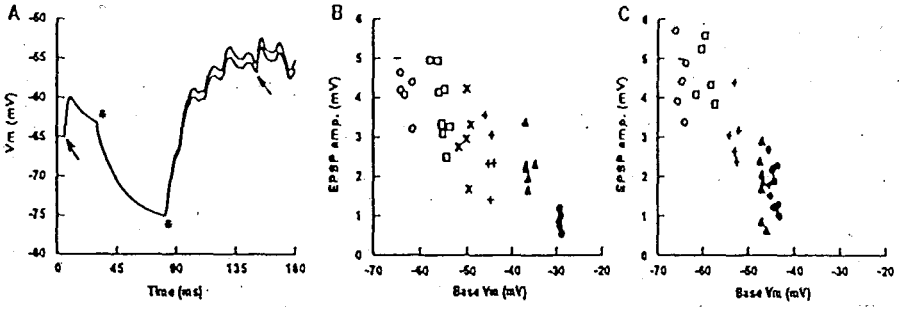

Figure 1. Dendritic saturation during simulated physiological synaptic activation of a layer 2 pyramid. (A) Somatic membrane potential (V_m) during simulation. A constant current of -0.1 nA is injected at t = 30 ms to prevent firing (first asterisk), then 70 excitatory synapses are activated at a mean frequency of 50 Hz to simulate visual stimulation (second asterisk). 35 additional synapses are given a simultaneous stimulus to produce a control (first arrow) and test (second arrow) EPSP. The amplitude of the test EPSP is significantly reduced with respect to the control. Upper trace is result of simulation with all excitatory synapses directly on dendritic shafts, lower trace is result of simulation with all synapses on the heads of dendritic spines. (B) Peak amplitude of the test EPSP plotted against V_m just before the EPSP occured, for a variety of firing frequencies of the 70 excitatory synapses; * = 0 Hz, E = 25 Hz, G = 50 Hz, I = 75 Hz, D = 100 Hz, C = 200 Hz, F = 300 Hz, J = 400 Hz. The amplitude of the EPSP decreased linearly with V_m. (C) Concurrent inhibition is included in the simulation (33 inhibitory synapses at twice frequency of excitatory synapses).

We have simulated Ferster's experiment to test this hypothesis using a digitised model layer 2 pyramid, simulated as a 400 compartment model using CABLE [4]. 70 excitatory synapses (each 0.5nS peak conductance) were placed randomly on the basal/oblique dendrites, and were activated at a mean frequency (eg. of 200Hz) at 80ms. A constant current of -0.1nA was injected starting at 30ms to prevent firing

during the synaptic activation. 35 additional excitatory synapses were placed on the same dendritic segments as the initial 70, and were given a single simultaneous stimulation at 5ms and again at 150ms. The firing of these 35 synapses represented the effects of electrical stimulation of the LGN - the first stimulation gave a control EPSP, the second, occuring during 'visual stimulation', gave a test EPSP. Different trials could be produced by using a different seed for the random number generator that produced the Poisson-distributed trains of EPSPs. We found that the test EPSP was significantly reduced with respect to the control EPSP. Figure 1 shows the peak height of the test EPSP plotted against the somatic membrane potential just before the EPSP occurs, for a variety of input frequencies.

In order to produce a steep enough slope on this graph, 33 inhibitory synapses (12 somatic, others on preterminal dendrites) were active concurrently with the 70 excitatory ones. This is consistent with physiological results showing that inhibitory input to excitatory cortical cells is weak during null responses and is in fact strongly correlated with the degree of synaptic activation of the excitatory cells [5]. This is also consistent with microanatomical data indicating that excitatory cells make direct contacts with inhibitory cells, which then make direct contacts back onto the same excitatory population [6].

15.2 EFFECTIVENESS OF INHIBITION

When we added active conductances to the above model to produce adapting trains of action potentials, we found that the inhibition produced by 33 synapses significantly reduced the firing rate when the inhibitory synapses were discharging at a high rate (800Hz). Cortical pyramidal cells receive hundreds of inhibitory synaptic contacts on their somata and proximal dendrites [7]. Therefore, we increased the number of active inhibitory synapses in our simulation to determine if the concerted activity of a larger fraction of the cell's inhibitory input was sufficient to suppress firing. We found that the activity of about 200 somatic inhibitory synapses is sufficient to prevent a cell that is receiving strong excitation from firing. Consequently, we conclude that strong cortical inhibition is able to prevent the firing of even strongly driven pyramidal cells, contrary to previous conclusions [8].

The input resistance (R_{in}) of cortical neurons shows no significant reduction during the response to nonpreferred stimuli or even during sustained hyperpolarizations that are part of an optimal response to a visual stimulus [9],[3]. Tests of our model show that R_{in} decreases by at least 50% during the simulations using only 33 inhibitory synapses. This indicates that the level of inhibition used in our simulations was as least as great as the level of inhibition occuring during null or hyperpolarizing visual responses. This level of inhibition was not strong enough to suppress significant synaptic excitation. Consequently, the reason that the cell is not firing at these times must be because of a lack of synaptic excitation.

15.3 REDUCED COMPARTMENTAL MODELS

Further research into the synaptic activation of cortical cells will require the simulation of the network which is providing that activation. At present the speed of available computers is such that 400 compartment models are too large to be used in network simulations. Most model neurons composed of just a few compartments have been assigned a somewhat arbitrary geometry, with no systematic testing of the reduced model against the real cell or a more complete model. Such models may have the same R_{in} and time constant as the real cell, but typically will not accurately simulate the integration of inputs from the dendritic compartments into the soma. We have produced a 9 compartment model that faithfully reproduces the performance of the full 400 compartment model.

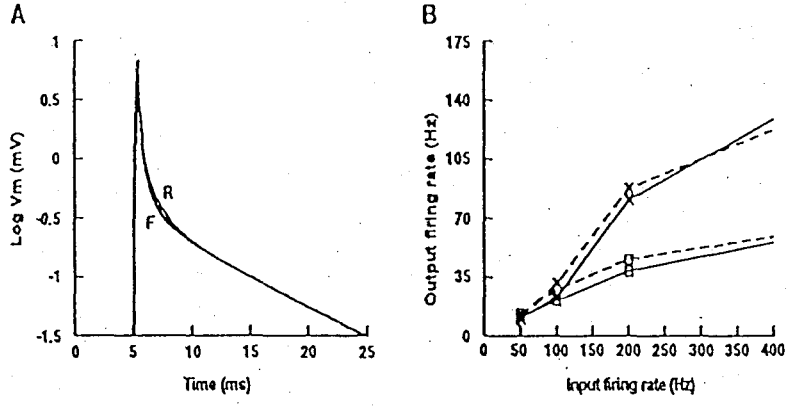

Figure 2. A) Semi-log plot of voltage response of reduced (R) and full (F) model layer 2 pyramidal cells to a 0.44 ms 0.3 nA somatic current injection at t = 5 ms. B) Comparison of firing rates of reduced (dashed traces) and full (solid traces) model layer 5 cells as a function of the firing rate of their 140 excitatory inputs. The somata of both models contain active conductances with exactly the same kinetics and densities. Each model also receives 45 inhibitory synapses, active at twice the rate of the excitatory ones. I = Initial, peak firing rate. G = Steady, adapted firing rate. The close fit of the two models demonstrates that the reduced model integrates excitatory and inhibitory synaptic input in the same manner as the full model.

The 'equivalent dendritic profile' [1] conserves surface area but at the expense of axial resistance - the equivalent dendrite is too wide and does not produce significant attenuation of synaptic input. Our approach is to conserve axial resistance by setting the diameter of the equivalent cylinder to a value such that the reciprocal of the axial resistance of the equivalent cylinder is equal to the sum of the reciprocals of the axial resistances of all the dendrites represented by that equivalent cylinder. The length of the equivalent cylinder is just the average length of all the dendrites represented by the equivalent cylinder. The membrane resistance and capacitance are then scaled for the loss in membrane area by matching the R_{in} and time constant with that of the full

model. The resulting reduced model not only has the same R_{in} and time constant as the full cell, but also gives the same voltage response to a brief somatic current pulse [1], which depends on the rate of flow of current from soma to dendrites (Figure 2). When active conductances are taken from the full model and put directly into the reduced model, both models show almost exactly the same firing response to identical dendritic synaptic input. This means that the reduced model has the same E-S coupling characteristics as the full model.

REFERENCES

1. Stratford, K., A. Mason, A. Larkman, G. Major and J. Jack. "The modelling of pyramidal neurons in the cat visual cortex." The Computing Neuron. Durbin, Miall and Mitchison ed. 1989 Addison-Wesley. Wokingham, England.

2. Rinzel, J. and W. Rall. Transient response in a dendritic neuron model for current injected at one branch. Biophys. J. 14: 759-789, 1974.

3. Ferster, D. and B. Jagadeesh. EPSP-IPSP interactions in cat visual cortex studied with *in vivo* whole-cell patch recording. J. Neurosci. 12: 1262-1274, 1992.

4. Hines, M. L. A program for simulation of nerve equations with branching geometries. Int. J. Biomed. Comp. 24: 55-68, 1989.

5. Ferster, D. Orientation selectivity of synaptic potentials in neurons of cat primary visual cortex. J. Neurosci. 6: 1284-1301, 1986.

6. Douglas, R. J., K. A. C. Martin and D. Whitteridge. A canonical microcircuit for neocortex. Neural Comp. 1: 480-488, 1989.

7. Farinas, I. and J. DeFelipe. Patterns of synaptic input on corticocortical and corticothalamic cells in the cat visual cortex. I. The cell body. J. Comp. Neurol. 304: 53-69, 1991.

8. Douglas, R. J. and K. A. C. Martin. Control of neuronal output by inhibition at the axon initial segment. Neural Comp. 2: 283-292, 1990.

9. Douglas, R. J., K. A. C. Martin and D. Whitteridge. Selective responses of visual cortical cells do not depend on shunting inhibition. Nature. 332: 642-644, 1988.