Summation and Division by Neurons in Primate Visual Cortex

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been digested to completion with Bam HI; these libraries were screened with a probe correspond- ing to sequences within the transgene. The wild- type clones (D'3 and E'4) corresponding to the transgene insertion site were cloned by screening of a wild-type FvBN partial Sau 3A-ag digested genomic library with HRA, an internal Eco RI fragment from pA46-7.6 that contains se- quences flanking the transgene insertion. Total RNA was isolated by use of the guanidinium isothiocyanate procedure (28) and enriched for polyadenylated [poly(A)]+ RNA by passage through oligo(dT) columns. The cDNA library was prepared from poly(A)+ RNA isolated from whole 14.5 days post-collum (dpc) mouse embryos; Smal adaptors and Eco RI ends were added and the double-stranded cDNAs ligated into the Xgt10 vector (Stratagene). Hybridization probes were labeled with [α-32P] deoxythymidine triphosphate (dCTP) by the random-hexamer labeling method (29). The Sanger dyeodeoxyx nucleotide method was used for all sequencing (30).

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Recordings from monkey primary visual cortex (V1) were used to test a model for the visually driven responses of simple cells. According to the model, simple cells compute a linear sum of the responses of lateral geniculate nucleus (LGN) neurons. In addition, each simple cell's linear response is divided by the pooled activity of a large number of other simple cells. The cell membrane performs both operations; synaptic currents are summed and then divided by the total membrane conductance. Current and conductance are decoupled (by a complementary arrangement of excitation and inhibition) so that current depends only on the LGN inputs and conductance depends only on the cortical inputs. Closed form expressions were derived for fitting and interpreting physiological data. The model accurately predicted responses to drifting grating stimuli of various contrasts, orien- tations, and spatiotemporal frequencies.

Since the pioneering work of Hubel and Wiesel (1), there have been a multitude of physiological experiments that studied the visually driven responses of V1 simple cells. A long-standing view is that a simple cell's response depends on a linear sum, over local space and recently past time, of the intensity values in the stimulus (2). The linearity of simple cell physiology is attractive because the response of a linear cell can be completely characterized with a relatively small number of measurements. In addition, the linear model explains the selectivity of simple cells for stimulus position, orientation, and direction of motion.

Unfortunately, the linear model fails short of a complete account of simple cell physiology. According to the linear model, doubling the contrast of a (periodic) drifting grating stimulus would double the re-
tances that vary over time depending on the firing rates of the presynaptic cells. The membrane potential changes over time, given the present value of the membrane potential and the present synaptic conductances

\[ \frac{dV}{dt} = g_e(V_e - V) + g_i(V_i - V) + g_{shunt}(V - V_{shunt}) + g_{leak}(V - V_{leak}) \]

where \( I_d = g_eV_e + g_iV_i + g_{shunt}V_{shunt} + g_{leak}V_{leak} \)

and where \( C \) is the membrane capacitance, \( V_e, V_i \), and \( V_{shunt} \) are excitatory, inhibitory, and shunt equilibrium potentials, respectively, \( g_e, g_i \), and \( g_{shunt} \) are the variable conductance resistors, and \( g_{leak} \) and \( V_{leak} \) determine the leak current. We define \( I_d \) to be the cell's driving current; it has the units of current and depends on the cell's synaptic inputs but is independent of the cell's membrane potential \( V \). The driving current can be measured by voltage-clamping the cell at \( V = 0 \).

Solving Eq. 1 yields an expression for the cell's membrane potential as a function of the synaptic conductances (7)

\[ V = \left[ \frac{\theta}{C} \exp\left(\frac{-t}{\theta}\right) \right] \ast \left[ \frac{I_d}{C} \right] \]

where \( \theta = 1 \) if time \( t > 0 \) and \( \theta = 0 \) otherwise. Equation 2 is a typical textbook formulation of the synaptic input to a neuron. The membrane potential \( V \) is equal to the driving current, \( I_d \), divided by the total conductance, \( g \), and then convolved with an exponential low-pass filter. The relation between the membrane potential and the instantaneous firing rate, \( R \), can be approximated (8) by half-wave rectification followed by squaring

\[ R = \max(0, V - V_{thres})^2 \]

where \( V_{thres} \) is the membrane potential in the absence of visual stimulation.

To develop a biophysical mechanism that performs both summation and division, we postulate that there are two sets of inputs: the "linear" synaptic conductances and the "normalization" synaptic conductances. The linear synapses regulate \( g_e \) and \( g_i \), and are contributed by neurons in the lateral geniculate nucleus (LGN). The normalization synapses regulate \( g_{shunt} \), and are contributed by all the cortical neurons in the normalization pool. In addition, we postulate that the equilibrium potential of the normalization synapses, \( V_{shunt} \), is equal to a cell's resting potential (9). For simplicity of notation, we chose \( V_{thres} = V_{shunt} = 0 \) and specified all other voltages with respect to this origin. Finally, we postulate that the linear inputs trade off against one another:

\[ g_e + g_i + g_{leak} = 0 \]

where \( g_{leak} \) and \( g_i \) are constants. When there is no visual stimulation, the cell's conductance equals \( g_i \), partly a result of the spontaneous activity of the presynaptic cells and partly because the membrane has nonzero conductance. Equation 4 is the key property of our model because it allows us to decouple current from conductance. Changes in the cell's total conductance, \( g \), depend only on the normalization inputs (because \( g_i \) is a constant), and changes in the driving current, \( I_d \), depend only on the linear inputs (because \( V_{shunt} = 0 \)). One could implement Eq. 4 by having a complementary arrangement of inputs: \( g_e \) could be driven by on-center LGN cells and \( g_i \) by off-center LGN cells with spatially superimposed receptive fields (Fig. 1). In this way, an increase in the excitatory conductance from the LGN would be matched by a decrease in the inhibitory conductance and vice versa (10).

Our model achieves normalization because a cell's conductance depends on the total activity of all the cells in the normalization pool. Changing the conductance, \( g \), has two effects on the membrane potential: (i) It changes the gain (sensitivity to input) because the cell's driving current is scaled by conductance and (ii) it changes the dynamics because the cell's time constant \( (C/g) \) is also scaled by conductance (Eq. 2).

To test the model, we recorded the responses of simple cells in anesthetized paralyzed macaque monkeys (11) while presenting drifting sinusoidal gratings of various contrasts, orientations, and spatial frequencies. We used the normalization model to fit the amplitude and phase of the first harmonic of the responses. According to the model, increasing stimulus contrast should yield an increase in membrane conductance that, in turn, should yield a decrease in gain (response amplitude saturation) and a decrease in the time constant (response phase advance).

Results for a typical cell are shown in Fig. 3; similar results were obtained for nine other cells. As predicted by the model, response amplitude saturates and response phase advances with increasing contrast. By comparison, the response phase of a linear cell would be constant and the response amplitude of a linear cell would not saturate.

Our model explains another important aspect of the responses: Amplitude saturation and phase advance do not depend on stimulus orientation. In Fig. 3E, the two response amplitude curves (for preferred and nonpreferred orientations) are vertically shifted copies of one another; because the data are plotted on a logarithmic response scale, this means that the ratio of response amplitudes is about the same at all stimulus contrasts. Likewise, in Fig. 3F, the difference in response phases does not depend on contrast. These invariances, which we attribute to normalization, are critical for encoding information about orientation independent of contrast. Similar vertical shifts of log response amplitude versus contrast have been reported for stimuli of nonpreferred spatial frequency and direction of motion (3, 12). The vertical shift of response phase has not been reported previously.

For 7 of our 10 cells, we measured responses at different temporal frequencies.
Fig. 3. One cycle of the response of a V1 simple cell to drifting sinusoidal gratings of contrast 0.125, 0.25, 0.5, and 1.0, respectively; temporal frequency was 3 Hz. The response amplitude saturation is evident because stimulus contrast doubles from C to D, but height does not double. The response phase advance is evident because the peak in (D) is almost 50 ms earlier than that in (A). (E and F) Amplitude and phase of the fundamental Fourier component of the response of a V1 simple cell to drifting sinusoidal gratings that varied in contrast and orientation.

This cell was tested with 90 randomly interleaved stimuli (three temporal frequencies, three orientations, and 10 contrasts). Here we show only the responses for one temporal frequency (6 Hz) and for two orientations: preferred orientation (open symbols) and 20° from the preferred orientation (filled symbols). Error bars represent ±1 SD (n = 5). The continuous curves in each plot show the best fit of our model. The model is mathematically tractable, enabling us to derive closed form expressions for fitting and interpreting physiological data. Response amplitude as a function of stimulus contrast c and stimulus temporal frequency ω is given by

\[ \text{amplitude}(R) = \frac{C^2}{g^2 + (\omega C)^2} \]

where C is capacitance, g = \sqrt{g_{\text{R}}^2 + kC^2} (conductance), and g, K, and k are constants. Response phase is given by phase(R) = \phi + arctan(\omega C/g) where \phi is another constant. The free parameters of the fit are the response gain and phase (K and \phi, different for each orientation and temporal frequency) of the underlying linear stage, the time constant of the membrane at rest (C/g), and the strength of the normalization signal (K/g).

and used the model to estimate the time constant of the membrane (that is, membrane capacitance divided by membrane conductance). The estimated time constant at rest (zero contrast) varied in our cells from 0 to 98.5 ms (mean = 27.8 ms). These values are consistent with published intracellular measurements (13). The estimated membrane time constant decreased on average by a factor of 3.7 ± 0.7, when contrast was increased from 0 to 1. In other words, we predict that the conductance of a simple cell should increase about fourfold when the cell is presented with a full contrast grating and that this conductance increase should be independent of stimulus orientation (14, 15).

Simple cells have a limited dynamic range, a limit to how strong an output signal they can generate and, hence, a limit to the range of contrasts over which they can respond differentially. Normalization makes it possible for response ratios to be independent of stimulus contrast (shown by the vertical shift of the curves in Fig. 3E), even in the face of response saturation. This invariance is critical for encoding visual information (about motion, orientation, binocular disparity, and other factors) independent of contrast. Normalization thus preserves the essential features of linearity in a system, that of the brain, that has limited dynamic range. Although there is direct empirical support for the complementary arrangement of the linear summation inputs in our model (10), our mechanism for division is not consistent with recent intracellular measurements that show (i) slight conductance increases (16) and (ii) no indication that membrane potential is normalized (17). We could reconcile our model with these intracellular results by proposing a variation of the model that yields the same (firing rate) response without corresponding conductance increases. This second model still has a complementary arrangement of inputs to perform linear summation, but it uses a different mechanism for division. We have been assuming that the transformation between membrane potential and firing rate is not affected by the visual stimulus and that division is implemented by changing conductance. Instead, division might be implemented by changing the gain of the firing mechanism. Further intracellular measurements could clearly distinguish between these two possibilities.

REFERENCES AND NOTES

7. This solution is exact when the total conductance is constant over time. It is an approximate solution when the total conductance varies slowly over time. For simplicity, we dropped the term that corresponds to the initiation of firing.
8. Firing rate is proportional to membrane depolarization, once above threshold [C. E. Stafstrom, P. C. Schwindt, W. E. Crill, J. Neurophysiol. 52, 1051 (1984)]. To simplify the mathematics, we approximate the threshold by half-wave rectification and squaring

\[ V = \frac{m(V_{\text{rest}} - V_{\text{threshold}})}{V_{\text{threshold}} - V_{\text{rest}}} \]

where m is a constant and V_{\text{threshold}} is the spike threshold. This approximation is reasonable because (i) V_{\text{rest}} < V_{\text{threshold}} (simple cells typically have no spontaneous activity) and (ii) the relevant range of membrane potentials is limited.

9. Shunting inhibition is a widely cited proposal for how neurons might perform division [J. S. Coombs, J. C. Eccles, P. Fatt, J. Physiol. (London) 196, 395 (1968); C. Koch and T. Poggio, in Synaptic Function, G. M. Edelman, W. E. Gall, W. M. Cowan, Eds. ( Wiley, New York, 1987), pp. 637-698]. Because the equilibrium potential for chloride, V_{\text{Cl}}, is close to a cell’s resting potential, opening chloride channels will change the cell’s conductance without introducing much current. Chloride shunting, however, only approximates division because V_{\text{Cl}} is not exactly equal to V_{\text{threshold}}. Exact division can be implemented with two synaptic conductances, one excitatory and one inhibitory, that increase (or decrease) in proportion such that

\[ \frac{g_{\text{E}}V_{\text{E}} + g_{\text{Cl}}V_{\text{Cl}}}{\text{V}} = \frac{g_{\text{E}} + g_{\text{Cl}}}{\text{V}} \]

where \lambda is a constant (note that V_{E} and V_{Cl} have opposite sign). This pair of channels has an effective equilibrium potential and a conductance

\[ \frac{g_{\text{E}} + g_{\text{Cl}}}{\text{V}} \]


11. Together with J. A. Movshon, L. P. O’Keefe, and C. Tang, we recorded the extracellular activity of cells in the primary visual cortices of three paralyzed and anesthetized macaque monkeys. Our results are from 10 cells that were chosen out of 106 for the following reasons: (i) they were readily classified as simple cells; (ii) they were tested at least twice; and (iii) they showed satisfactory stability and isolation for the duration of the test (>1 hour). All cells were tested with a variety of contrasts and orientations (or spatial frequencies). Seven of the 10 were also tested with different temporal frequencies.

14. A fourfold increase in conductance is not inconceivable; computer simulations of a pyramidal cell [O. Bernander, R. J. Douglas, K. A. C. Martin, C.
An Increased Percentage of Long Amyloid β Protein Secreted by Familial Amyloid β Protein Precursor (βAPP<sub>717</sub>) Mutants

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Normal processing of the amyloid β protein precursor (βAPP) results in secretion of a soluble 4-kilodalton protein essentially identical to the amyloid β protein (Aβ) that forms insoluble fibrillar deposits in Alzheimer's disease. Human neuroblastoma (M17) cells transfected with constructs expressing wild-type βAPP or the βAPP<sub>717</sub> mutants linked to familial Alzheimer's disease were compared by (i) isolation of metabolically labeled 4-kilodalton Aβ from conditioned medium, digestion with cyanogen bromide, and analysis of the carboxyl-terminal peptides released, or (ii) analysis of the Aβ in conditioned medium with sandwich enzyme-linked immunosorbent assays that discriminate Aβ<sub>1-40</sub> from the longer Aβ<sub>1-42</sub>. Both methods demonstrated that the 4-kilodalton Aβ released from wild-type βAPP is primarily but not exclusively Aβ<sub>1-40</sub>. The βAPP<sub>717</sub> mutations, which are located three residues carboxyl to Aβ<sub>43</sub>, consistently caused a 1.5- to 1.9-fold increase in the percentage of longer Aβ generated. Long Aβ (for example, Aβ<sub>1-42</sub>) forms insoluble amyloid fibrils more rapidly than Aβ<sub>1-40</sub>. Thus, the βAPP<sub>717</sub> mutants may cause Alzheimer's disease because they secrete increased amounts of long Aβ, thereby fostering amyloid deposition.

The 39– to 43-amino acid polypeptide Aβ, deposited as amyloid (1, 2) in the brains of patients with Alzheimer's disease (AD), is derived from a set of 677 to 770 amino acid proteins collectively referred to as βAPP (2–4). Strong evidence that amyloid deposition plays a critical role in the development of AD has come from the identification of familial AD (FAD) kindreds in which the AD phenotype cosegregates with mutations in the βAPP gene. Three of the FAD-linked βAPP mutations convert the valine located three residues carboxyl to Aβ<sub>3</sub> (Val<sup>17</sup> in βAPP<sub>717</sub>) to isoleucine ([I] (5), phenylalanine ([F] (6), or glycine ([G]) (7). A fourth double mutation ([NL]) alters the lysine-methionine located immediately amino to Aβ<sub>3</sub> (Lys<sup>370</sup>Met<sup>371</sup> in βAPP<sub>717</sub>) to asparagine-leucine (8). The location of these mutations immediately suggests that they may cause AD by altering βAPP processing in a way that is amyloidogenic.

Cells expressing βAPP<sub>695NL</sub> secrete five to six times more 4-kDa Aβ than those expressing wild-type βAPP (9, 10). Thus, βAPP<sub>695NL</sub> undergoes altered processing that enhances the likelihood of amyloid deposition. Transfected cells expressing βAPP<sub>695NL</sub> do not, however, release increased amounts of Aβ (9). To account for this observation, we proposed (9) that the FAD-linked mutations on the carboxyl side of Aβ ([D], [F], [G]) shift cleavage to favor generation of longer Aβs such as Aβ<sub>1-40</sub> or Aβ<sub>1-42</sub>. Because these longer Aβs form amyloid fibrils more rapidly than Aβ<sub>1-40</sub> (11, 12), shifting the site of cleavage could result in amyloid deposition without increasing the overall amount of Aβ produced. Here we have used two different methods to test this hypothesis.

Our initial approach was to label transfected M17 cells with [35S]methionine plus either [3H]valine or [3H]leucine. The radioisotopically labeled Aβ in conditioned medium was then separated by immunoprecipitation and tris-tricine SDS–polyacrylamide gel electrophoresis (PAGE) as previously described (13), transferred to immobilon, visualized autoradiographically, and excised. The excised 4-kDa Aβ was digested with cyanogen bromide (CNPb), which cleaves Aβ on the carboxyl side of the methionine at Aβ<sub>40</sub>, releasing COOH-terminal peptides beginning at Aβ<sub>40</sub> (for example, Aβ<sub>36-40</sub> from Aβ<sub>1-40</sub>). Finally, the radioiodolated CNBr peptides were separated by reversed-phase liquid chromatography (RPLC) with a Vydac narrow bore C4 column. CNBr digestion was carried out in the presence of excess unlabeled Aβ<sub>36-40</sub> and Aβ<sub>36-42</sub> both to improve recovery of the labeled COOH-terminal peptides and to mark, by ultraviolet absorption, the fractions in which Aβ<sub>36-40</sub> and Aβ<sub>36-42</sub> elute.

The radioactively labeled COOH-terminal peptides that CNBr releases from the 4-kDa Aβ produced by M17-BAPP<sub>695</sub> cells labeled with [35S]methionine plus [3H]valine are shown in Fig. 1A. The major radiolabeled peptide eluted from the C4 column with unlabeled Aβ<sub>36-40</sub>. In addition, there was minor labeled peptide that eluted with unlabeled Aβ<sub>36-42</sub> (14). To further characterize these COOH-terminal peptides, we examined the large amount of 4-kDa Aβ released from M17-BAPP<sub>695NL</sub> cells labeled with [35S]methionine plus either [3H]valine or [3H]leucine (Fig. 1B). We identified the major COOH-terminal peptide released from this 4-kDa Aβ by CNBr digestion as Aβ<sub>36-40</sub> by radiosequencing it to show valine residues at positions 1 and 4 as expected (15), (ii) demonstrating (Fig. 1B) that it is not labeled by [3H]leucine and therefore terminates be-