

The role of single neurons in information processing

Christof Koch¹ and Idan Segev²

¹Computation and Neural Systems Program, Division of Biology, 139-74, California Institute of Technology, Pasadena, California 91125, USA

²Department of Neurobiology and Interdisciplinary Center for Neural Computation, The Hebrew University, Jerusalem 91904, Israel

Correspondence should be addressed to C.K. (koch@klab.caltech.edu)

Neurons carry out the many operations that extract meaningful information from sensory receptor arrays at the organism's periphery and translate these into action, imagery and memory. Within today's dominant computational paradigm, these operations, involving synapses, membrane ionic channels and changes in membrane potential, are thought of as steps in an algorithm or as computations. The role of neurons in these computations has evolved conceptually from that of a simple integrator of synaptic inputs until a threshold is reached and an output pulse is initiated, to a much more sophisticated processor with mixed analog-digital logic and highly adaptive synaptic elements.

Neurons as point-like, linear threshold units

In 1943, McCulloch and Pitts¹ showed how a collection of simple, interconnected neuron-like units could process information. For reasons of analytical tractability, their view of neuronal processing is a stark, simple one. All synaptic inputs converge onto a single compartment ('point neuron'). Each synapse is modeled by a positive number, its synaptic weight. The activity of each presynaptic fiber (originally assumed to be either on or off) is multiplied by its associated synaptic weight and summed over all inputs. This sum is then compared against a threshold. If the threshold is exceeded, and if no inhibitory unit is active, the neuron generates a spike and sends it on to its postsynaptic targets. Otherwise, the cell remains quiet. McCulloch and Pitts proved that a sufficiently large number of these simple logical devices, wired together in an appropriate manner, are capable of universal computation. That is, a network of such 'linear threshold' units with the appropriate synaptic weights can perform any computation that a digital computer can, though not as rapidly or as conveniently.

Linear threshold model 'neurons' come in many flavors. The earliest originated in the early years of the 20th century, far before the biophysics of action potentials was understood, as 'integrate-and-fire' neurons. The state of the neuron is given by the voltage across a capacitance, with each synaptic input adding to or subtracting from the charge accumulating across the membrane (Fig. 1a). The voltage trajectory executes a random walk, depending on the nature of the synaptic input, until a fixed voltage threshold is reached. At this time, a unit pulse is generated, and the voltage is reset, that is, all charge is instantaneously removed from the capacitance. The output of this integrate-and-fire neuron consists of a train of asynchronous pulses. In a 'leaky' integrate-and-fire unit, an ohmic resistance is added in parallel to the capacitance, accounting for the loss of synaptic charge via the resistor and, consequently, the decay of the synaptic input with time (Fig. 1b).

In a 'rate neuron', the discrete output pulses are replaced by a continuous activation function, $g(V)$, that increases monotonically as a function of the activity, V . The stronger the excitatory input, the higher the output rate, f , of the neuron (Fig. 1c). The activation function $g(V)$ is sometimes identified with the cell's frequency-current relationship (f - I curve). Conceptually, such a graded

neuron encodes the inverse of the interspike interval of a population of spiking cells; that is, its activity represents the average firing frequency or rate of this group.

Common to these single cell models and their close relatives studied by neural network researchers² is, first, linear preprocessing of synaptic inputs—implying that inputs do not interact with each other in any 'interesting' way—and, second, a threshold computation (Fig. 1d). The computational power of these networks resides in the nonlinearity provided by the threshold. This is related to a logical AND operation: the threshold can be adjusted such that the cell will fire only if two inputs are simultaneously active. Put enough such units together and anything that is computable can be computed by such a network. Networks containing hundreds or thousands of such units that utterly neglect the geometry of real neurons are commonly used in pattern recognition (for example, to predict credit card fraud) and at most brokerage houses today.

Passive dendritic trees enhance computational power

If neurons can be reduced to a single compartment, why aren't all neurons spherical? We still do not fully understand the diversity of dendritic morphology in terms of its functional consequences (Fig. 2). It is likely that the sizes of the axonal and dendritic trees relate to wiring economy, that is, the principle that because space is at a premium, wiring length must be kept to a minimum³. Another constraint surely must be the cell's ability to receive input from specific recipient zones (for example, reaching all the way into superficial layers). Yet it is unclear to what extent these considerations explain the strikingly different dendritic morphologies (Fig. 2), once size is accounted for.

A lack of theoretical concepts as well as experimental tools for investigating dendrites led—with a few exceptions⁴—to their relative neglect for most of the 1950s and 1960s. A new area of dendritic physiology was ushered in by the widespread adoption of intracellular recordings and brain slices⁵ and by the development of the linear cable theory of dendrites by Rall⁶. Linear cable theory treats dendrites as core-conductor cables, surrounded by a passive membrane modeled by an ohmic conductance in parallel with a capacitance. When synaptic input is applied, such a cable acts as a low-pass filter, removing high temporal frequencies from the volt-

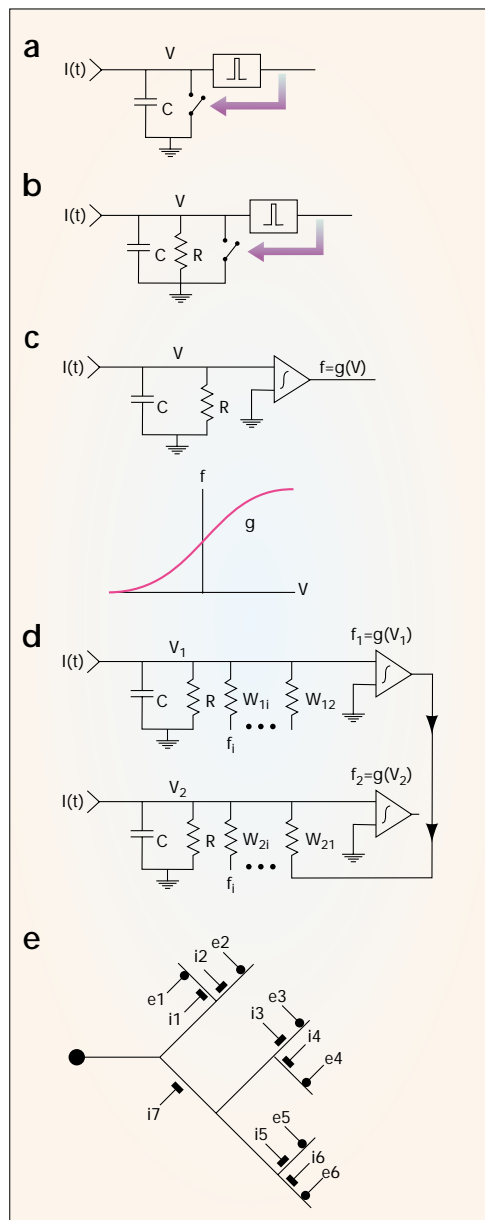


Fig. 1. Simple neuronal models. Electrical circuit idioms are often used to model neurons. In (a–d), the entire neuron is reduced to a single spatial compartment. The summed synaptic input is described by a net current $I(t)$. (a) An integrate-and-fire unit. If the voltage V exceeds a fixed threshold, an unit pulse is generated, and all charge on the capacitance is removed by resetting V to zero (solid arrow). The output of this and the leaky integrate-and-fire model (b; in which charge leaks away with a time constant given by the product of the capacitance C and the resistance R) is a series of asynchronous spikes. (c) In a rate neuron, these discrete pulses are replaced by a continuous output rate. The monotonically increasing relationship between V and the output rate $f = g(V)$ can be thought of as the discharge function of a population of spiking cells. (d) In most neural networks, interactions within neurons are linear. The necessary nonlinearity is provided by the sigmoidal $g(V)$ function. Here, the output of neuron 1 is unidirectionally connected to neuron 2 with synaptic weight w_{21} . (e) Nonlinear, saturating interactions can be mediated in a passive dendritic tree by synapses that increase the postsynaptic conductance. The interaction between excitation (circles) and inhibition of the shunting type (elongated boxes) is of the AND-NOT type and is specific in space and in time. For instance, the inhibitory synapse i_7 vetos excitation e_3 or e_6 but has only a negligible effect on e_1 . Modified from ref. 8.

synapses than for synapses located farther away⁷. As a consequence, local nonlinear operations can be performed independently in many dendritic subunits⁸ before the outputs of these local operations are summed up (and compared against the threshold) at the axon.

This sublinear effect is particularly strong for shunting or 'silent' inhibition, in which the synaptic reversal potential is close to the cell's resting potential. Without any other input, activation of shunting inhibition causes an increase in the local conductance without a change in the postsynaptic membrane potential. Depending on its amplitude, shunting inhibition can greatly reduce the amplitude of excitatory input. It acts to veto excitation, akin to an AND-NOT logical operation (that is, the output is high if excitation is present but inhibition is not; Fig. 1e). A neuron endowed with many such local synaptic circuits could, in principle, extract the motion, orientation or depth of a visual stimulus⁹. Although shunting inhibitory conductance changes were long thought to be too small to matter, modern intracellular recording techniques¹⁰ confirm their large magnitude in cortical cells. Intracellular evidence also implicates shunting inhibition in computing the direction of a moving stimulus in retinal ganglion cells¹¹, as proposed on theoretical grounds⁸.

A good example of how synaptic nonlinearity can combine with dendritic morphology to perform a specific computation is the first stage in the auditory pathway at which inputs from the two ears project to the same neuron¹². In the chicken, brainstem neurons with bipolar dendrites act as coincidence detectors, firing strongly if the sounds arrive at the two ears with some exact temporal delay, and much more weakly otherwise¹³. Excitatory synaptic inputs from the two ears are segregated, each ear mapping onto a single dendrite. Modeling shows that when input arrives from only one ear, strong synaptic saturation in the thin dendrite targeted by that ear can greatly reduce the synaptic current reaching the axon, so that the firing response is weak. In contrast, when inputs arrive simultaneously from the two ears, sufficient charge is delivered to the soma from the two dendrites acting semi-independently (thereby summing more linearly) that the neuron fires robustly. Modeling has confirmed that sensitivity to very small delays between the inputs, on the order of 20 μ s, is greatly enhanced by this setup compared to a point neuron with no dendrites¹⁴.

Active dendritic trees and nonlinear computations

It is abundantly clear that dendrites and their spines are covered by a plethora of excitable channel types, typically at a density of

age response to an input. Cable theory showed, and experiments bore out, that dendrites are electrically distributed rather than isopotential elements and that postsynaptic potentials, generated in the dendrites, undergo large voltage attenuation and significant temporal delay (on the order of the membrane's passive time constant) as they spread to the spike initiation zone.

What does add an important nonlinearity to neurons, and consequently could enrich their computational capabilities, is that synapses are not constant depolarizing or hyperpolarizing current sources. Rather, synaptic inputs transiently change the postsynaptic membrane conductance (for example, opening membrane ionic channels) in series with a battery (the synaptic reversal potential, whose value is determined by differential distribution of ions across the membrane and channel selectivity). Thus, a synaptic input briefly changes the electrical properties of the postsynaptic membrane. In particular, the postsynaptic potential (PSP) tends to saturate with stronger and stronger input. In passive dendrites, the PSP of two synapses is (typically) less than the linear sum of their separate responses. These saturation effects are more prominent for adjacent

10 or fewer channels per μm^2 of membrane, including voltage-dependent sodium, calcium and potassium channels^{15,16}. In many (but not all) cell types, the action potential actively propagates backward from the soma/axon region into the dendrites^{17,18}. Depending on the input conditions, action potentials can also be initiated in the dendrites by either synaptic input or the experimenter's electrode¹⁹. However, as expected from theory, such an action potential typically only propagates to a limited subregion of the tree, being extinguished by the large electrical load when approaching the low-impedance cell body region²⁰.

Much of the synaptic traffic is preferentially routed through dendritic spines, which cover the dendrites of many cell types, like thorns on a rose stem. The small dimensions of spines (with a volume on the order of $0.1 \mu\text{m}^3$) make them relatively inaccessible to prying eyes. Thus, until recently, their properties and function could only be analyzed with the aid of biophysical models^{21–23}. Early studies investigated the ability of spines to control synaptic weights by modulating the geometry of the thin elongated spine neck connecting the spine to its parent dendrite. Others focused on the logical threshold operations that could be performed by endowing spines with active properties that give rise to all-or-none electrical events²⁸. Subsequently, the attention of modelers turned to the isolation imposed on calcium and other intracellular messengers within the spine following synaptic input to either spine or dendrite. Two-photon imaging experiments have confirmed that calcium dynamics in the spine head can be isolated (by virtue of the extended spine neck) from events occurring in the parent dendrite²⁴. In particular, synaptic input induces a rapid influx of calcium that is restricted to the spine head. The amplitude and dynamics of this postsynaptic calcium increase is tightly controlled by many cellular processes. That is, spines constitute the smallest functionally independent chemical compartment, providing the substrate to implement temporally and spatially local learning rules, which might be restricted to single active synapses^{25,26}.

Equipped with a variety of voltage-gated channel types, dendrites with their distinct morphologies and large repertoire of synaptic inputs have the potential to be very powerful nonlinear computing devices. Unlike the sublinearity inherent to the summation of synaptic inputs, voltage-gated ion channels may generate nonlinearities that range from sublinear to highly supralinear responses. We now survey some of the best-explored proposals linking these operations to specific computations.

Synapse amplification and linearization

Sodium and calcium channels located at strategic points in the dendritic tree, such as spines or distal, thin processes, in conjunction with synapses expressing NMDA-type glutamate receptors, provide a powerful mechanism for boosting local synaptic inputs. In a typical dendritic tree, input impedances at distal arbors and spines increase from their relatively low values close to the cell body. Thus, distal excitatory synaptic inputs typically encounter favorable conditions for generating local regenerative responses and are amplified relatively more by the local excitable channels compared to synapses at more proximal sites.

A recent elegant study²⁷ demonstrates, in CA1 pyramidal neurons, that synaptic conductance changes become larger as one moves along the apical dendrite away from the soma. This progressive increase in synaptic amplitude seems to be primarily responsible for rendering EPSP amplitude at the soma insensitive to its origin.

Under certain conditions, synaptic input can trigger all-or-none dendritic action potentials. Theoreticians^{28,29} even envisioned a chain reaction of action potentials firing locally, between neighboring excitable spines and sibling branches in distal dendritic

arbors. Models show that the initiation of an action potential in the dendritic tree and the extent of its spread depend on the interplay among the strength, timing and location of the excitatory and inhibitory inputs, on the density and type of voltage-dependent channels and on dendritic morphology. The preferred direction of action potential propagation under physiological conditions and the degree of boosting of local inputs are being actively investigated^{18,20,30–32}.

'Handshake' between soma and dendrites

Fast-inactivating sodium channels in dendrites provide a means for an efficient electrical communication in the antidromic (soma-to-dendrite) direction. Because of these channels, the action potential can actively propagate from the spike-initiating zone in the axon back into distal dendritic zones rich with synapses. It thus provides a 'handshake' or acknowledgement signal by which synapses in these regions can know that an action potential has just been initiated at the axon. This can be critical to the Hebbian processes underlying associative synaptic plasticity^{33–35}. Markram and colleagues³³ controlled the relative timing of presynaptic and postsynaptic action potentials in a pair of excitatory coupled neurons, measuring its effect on the strength of synaptic coupling between the two cells. If the presynaptic spike preceded the postsynaptic one by as little as 10 ms, synaptic strength increased (long-term potentiation, LTP). Conversely, if the postsynaptic spike preceded the presynaptic one, synaptic coupling decreased (long-term depression, LTD). In other words, if the presynaptic cell is effective in triggering a spike in its postsynaptic target, the synapse is strengthened. If not, it is weakened. This sort of asymmetric (because $t_{\text{postsynaptic}} - t_{\text{presynaptic}} > 0$ favors LTP, whereas the reverse leads to LTD) synaptic plasticity mechanism can only be implemented because the postsynaptic site has access to the precise time of spiking via the backpropagated action potential³⁶. The mechanism is likely to involve a supralinear calcium influx at the postsynaptic site via relief of the voltage-dependent magnesium block of the NMDA receptor or amplification of the local EPSP by the backpropagating action potential.

Kistler and van Hemmen³⁷ proved how such a powerful Hebbian learning rule (see ref. 38 in this issue) leads, in an unsupervised manner, to strengthening those synapses that deliver

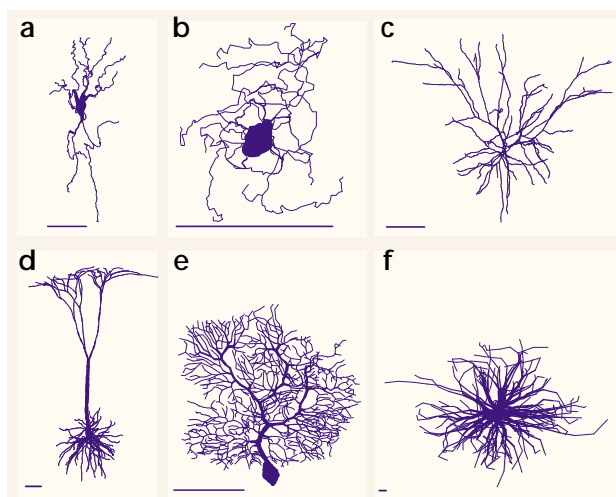


Fig. 2. Dendritic trees exist in many shapes and sizes. The dendritic trees of a vagal motoneuron (a), olivary neuron (b), layer 2/3 pyramidal cell (c), layer 5 pyramidal cell (d), Purkinje cell (e) and α motoneuron (f). Calibration bar = 100 μm . Reprinted with permission from ref. 55.

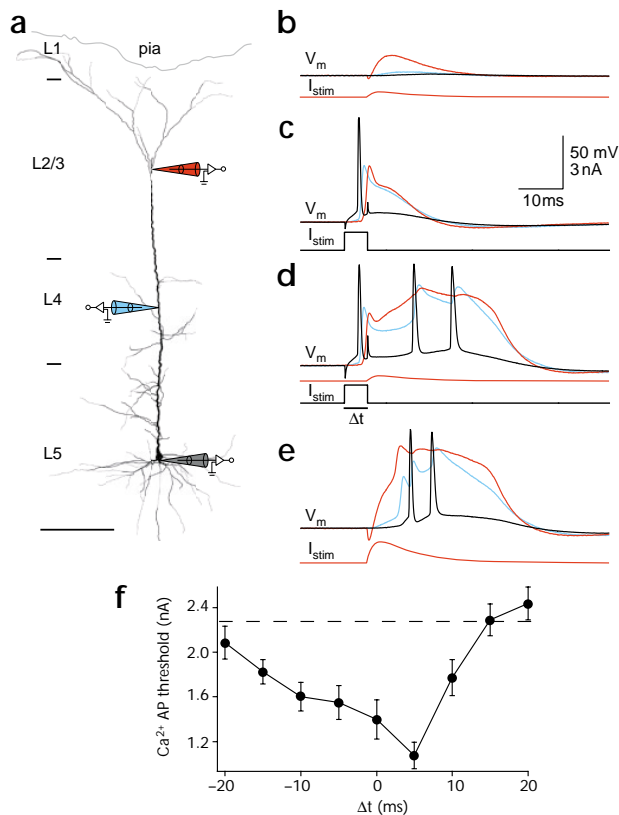


Fig. 3. Dendritic and axonal action potentials in a cortical pyramidal cell. Calcium-mediated action potentials in the dendrites give rise to a burst of fast, sodium-mediated axonal spikes. (a) Reconstructed pyramidal neuron with sites of electrode recordings (black, at soma; blue, 400 μm from soma; red, 770 μm from soma). Scale bar, 200 μm . (b) Current injection (I_{stim}) via the distal electrode on its own causes a subthreshold depolarization at the input (red trace, V_m) and the soma. (c) Somatic current injection gives rise to a local action potential (black trace), which propagates with decreased amplitude into the dendrite (blue and red traces). (d) Combining (b) and (c) injections—separated by 5 ms—evoked a burst of 3 sodium action potentials following the onset of a broad calcium spike in the distal dendrite (red). (e) Distal dendritic calcium spikes can be initiated by a stronger current input alone via the distal electrode. (f) The lowest current threshold needed to elicit a calcium spike (which then generates a burst of sodium spikes at the axon) is when the dendritic current injection follows initiation of the backpropagating action potential at the soma by 5 ms. Dashed line, threshold for calcium spike without backpropagating action potential. Each point is the average of eight neurons. Reprinted with permission from ref. 31.

of sodium spikes. In other words, a top-down signal would act in a modulatory manner to increase the saliency of a bottom-up signal by turning it from a single spike into a burst^{23,41,42}.

Multiplying in single neurons

Multiplication is both the simplest and one of the most widespread of all nonlinear operations in the nervous system. Along with the closely related operations of 'squaring' and 'correlation', multiplication lies at the heart of models for the optomotor response of insects and motion perception in primates. For instance, electrophysiological evidence from the monkey suggests that the discharge rate of neurons throughout visual cortex is up- or downmodulated by many factors, such as whether or not the animal is attending, the exact position of the eye in the orbit and so on. This modulation often takes the form of a multiplicative gain term that affects the strength of the cell's response, but not its tuning⁴³.

A number of different biophysical mechanisms could, in theory, implement a multiplicative algebra⁹. The one that seems most accessible to direct experimental investigation is responsible for mediating an escape response in the locust's visual system (Box 1). Another mechanism for achieving multiplicative interactions is synaptic clustering in dendrites endowed with NMDA, sodium and/or calcium channels^{44,45}. If the sole goal is to maximize the somatic PSP amplitude, then excitatory inputs into a passive tree should be spread out as much as possible to minimize synaptic saturation. This is not the case in dendritic trees containing significant voltage-dependent inward currents. Because of amplification, it pays to cluster synapses together on neighboring dendritic patches so that they can cooperate in activating the local excitable dendritic channels, thereby elevating the firing probability of the neuron. Formally, such a neuron approximates a low-order polynomial interaction in its synaptic input (of course, because of saturation, this is only true up to a point: placing all synapses at one location in the tree limits the maximal synaptic current delivered to the spike-initiating zone). That is, the firing rate of the neuron can be approximated by a sum of products over a subset of the synaptic inputs, turning the neuron endowed with such a mechanism into a more powerful computational engine than a passive neuron. Clustering is very robust to the details of the exact kinetic scheme, channel densities and dendritic morphology. Almost any boosting mechanism will do, as long as it is sufficiently local.

Synaptic clustering requires a learning rule that encourages simultaneously active synapses to cluster in adjacent dendritic regions, whereas uncorrelated synapses should have no privileged

precisely timed action potentials at the expense of synapses that receive spikes with a lot of temporal slop. In other words, given asymmetric Hebbian synaptic plasticity, a neuronal representation favoring coincident spikes (that is, temporal coding) can emerge in a natural manner.

Coincidence detection in active dendrites

A vigorous, ongoing debate surrounds the question of the temporal resolution at which information is represented by individual action potentials. Although it is clear that particular modules, such as auditory localization or pulse generation in electric fish, involve highly specialized circuits dedicated to preserving temporal information in the submicrosecond domain, it is far less clear to what extent, say, spiking cells in cortex can represent information with millisecond or better resolution. Biophysically plausible proposals for coincidence detection^{39,40} exploit fast sodium action potential generation in spines and distal basal dendrites to achieve submillisecond resolution but remain untested experimentally.

A convincing experimental example³¹ of dendritic coincidence detection at the 10-ms level (Fig. 3) occurs in layer-V pyramidal neurons; when a somatic-triggered action potential coincides with an excitatory input delivered to the apical dendrite, a powerful calcium action potential may be triggered locally in the apical dendrite. This long-lasting (10 ms or longer) calcium action potential evokes, in turn, a burst of sodium spikes generated at the axon (Fig. 3). The backpropagating sodium action potential serves as a 'binding' mechanism for a specific input combination in the dendritic tree.

Suppose a visual input triggers an action potential in a pyramidal cell in primary visual cortex. The fast sodium spike propagates both to its postsynaptic target cell and into the apical tree. If, at the same time, feedback input from extrastriate cortex depolarizes the distal apical tree, this might be sufficient to trigger a burst

Box 1. A model system to explore the biophysics of algebraic multiplication.

An experimentally accessible system for tracking down the biophysical substrate of multiplication is the lobular giant movement detector (LGMD) in the visual system of the locust. It is thought to be important in the detection and tracking of objects approaching on a collision course toward the animal⁵⁶. (a) The looming stimulus subtends an angular size $\theta(t)$ that increases nonlinearly with time (top; $d/v = 60$ ms). The intracellular recording shows how the LGMD tracks the object during approach. This cell integrates retinotopic motion-sensitive inputs impinging on one branch of its main dendritic branch (red in c; the approximate height of the dendritic tree is 300 μm) and receives feedforward, inhibitory projections sensitive to ON and OFF stimuli that depend on the angular size of the object on two dendritic compartments⁵⁷ (blue and magenta). The time course of LGMD's firing rate, $f(t)$, during the approach of an object is well described by multiplication of two terms related to the two main synaptic inputs impinging on LGMD's dendrites^{58,59}. The first term is proportional to the angular velocity of the expanding object, $\theta'(t)$ (the \prime stands for the temporal derivative of the object's angular size on the retina, θ), and the second one is a negative exponential of $\theta(t)$:

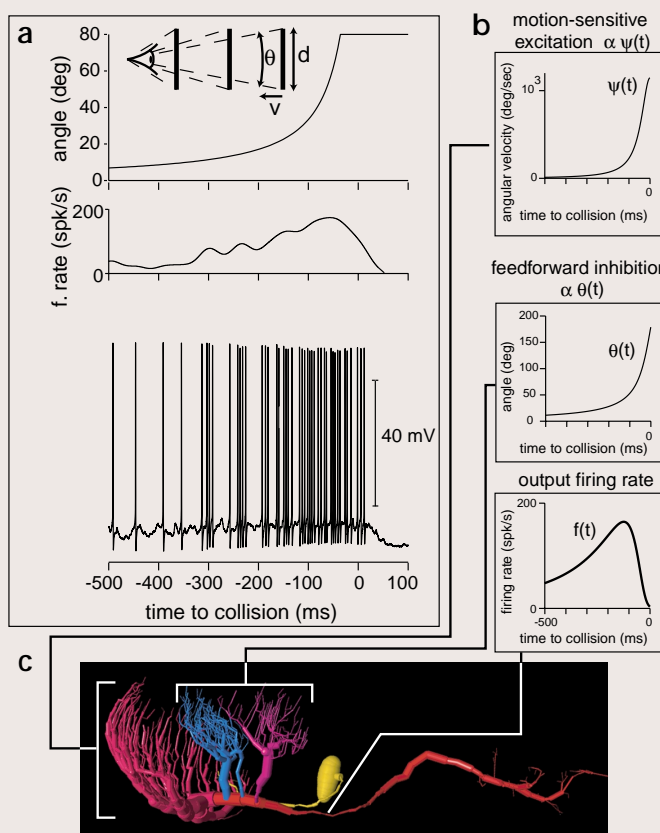
$$f(t) = \theta'(t - \delta) * e^{-\alpha * \theta(t - \delta)} \quad (1)$$

The δ implements a lag in the neuronal response. The $\theta'(t - \delta)$ term is always excitatory, because the angular edge velocity of an expanding object is positive during approach (b; with $\alpha = 5$, $\delta = 25$ ms, $d/v = 100$ ms). The $-\alpha * \theta(t - \delta)$ component acts as an inhibitory term, whose importance grows very rapidly as collisions looms because of its exponential dependence on image size. This equation reproduces the characteristic time course of the LGMD's firing rate during object looming: a rapid increase curtailed by an abrupt decrease toward the end of approach. It follows⁵⁹ that the peak in LGMD's firing rate always occurs a fixed delay δ (about 30 ms) after the object has reached a fixed angular size on the retina, independent of the speed of approach or the object's physical size. In the locust's brain, the spiking activity of LGMD is relayed to neurons that are involved in the generation of flight steering and jump escape behaviors.

The detailed biophysical mechanisms underlying this multiplication operation remain to be determined. An attractive possibility would be for the excitatory, motion-dependent input to be encoded in logarithmic coordinates and for the inhibitory input to be linear in angular size. If these two inputs induce depolarizing and hyperpolarizing currents in LGMD that add and are then exponentiated by local amplifying membrane properties of LGMD⁶⁰, the cell's firing rate would be given by Eq. 1. This is quite similar to the way analog electrical circuit engineers multiply two signals: logarithmically transform the two, add the result and then apply an exponential ($xy = e^{\log(x) + \log(y)}$).

spatial relationship to each other. That is, synapses that are correlated but are not spatially adjacent might not be selectively preserved or enhanced. Such a local learning rule departs only modestly from the broadly accepted principles of neural development that holds that synaptic connections are initially made at random and strengthened or weakened (and ultimately eliminated) based on some sort of correlation between pre- and postsynaptic signals. Only future experiments can tell whether the brain make use of this powerful and robust synaptic algorithm for both storing and processing, that is computing, information⁴⁶.

Mel, Ruderman and Archie⁴⁷ propose that such clustering is used at the level of a pyramidal cell in primary visual cortex to fashion an orientation-selective 'complex' cell, that is, a cell sensitive to the orientation of a line or bar placed anywhere in its receptive field. The neuron receives direct geniculate input that is clustered on its dendrites, giving rise to orientation tuning (synaptic input corresponding to the cell's optimal orientation clusters along the dendrites, whereas input associated with the orthogonal orientation is spread throughout the cell) and spatial invariance



(because clusters on different dendrites act independently of each other and carry visual information from different parts of the visual field). This is in contradistinction to the canonical model of Hubel and Wiesel⁴⁸, which has 'complex' cells arise from the spatial convergence of multiple 'simple' cells. The synaptic clustering model predicts that intracellular blockade of the sodium, calcium or NMDA channels underlying clustering will eliminate orientation tuning in this specific neuron. This remains to be tested.

Developing complex neurons

How can the nervous system adjust the types and densities of the dozen or more voltage-dependent ionic channels throughout the dendritic tree to support its computational power? Or, a seemingly more basic question, how is the density of potassium and sodium channels adjusted to give rise to the rapidly rising and decaying axonal action potential? Too much potassium current and the membrane potential is unlikely to ever spike. Not enough and repolarization might be so slow that the action potential would extend for many milliseconds. Because the densities required to

support rapid spiking depend on cellular morphology and local input impedance, it is extremely unlikely that this information is encoded genetically. Rather, channel densities need to be adjusted online, dynamically. And this 'hardware' should be adaptable if conditions in the sensory environment change (say, if the mean contrast of visual stimuli and the amount of contrast fluctuation around this mean were to change from one day to the next) to optimally signal the relevant features, given the limited bandwidth of spiking cells. All of these questions are related to, but different from, the more commonly considered issue of synaptic plasticity. Theoreticians have begun to consider such scenarios⁴⁹.

In the case of homeostasis, LeMasson, Marder and Abbott⁵⁰ introduced a simple feedback mechanism, in which channel density depends on the intracellular concentration of calcium ions, and thus on overall spiking activity. The intensity and temporal patterning of presynaptic input will thereby influence the degree of excitability of the postsynaptic cell. Stemmler and Koch⁵¹ derived a learning rule based on information theory that adjusts the density, midpoint activation and steepness of dendritic inward and outward currents to match the statistics of the synaptic input to the limited bandwidth provided by the cell's output. Such a learning rule allows the neuron to continually modify its voltage-dependent membrane conductances to maximize information transmission between synaptic input and firing output subject to various constraints (for example, high rates with their associated higher metabolic expenditures should be reserved for rare events; see also ref. 52).

Experimental evidence for plasticity in the intrinsic excitability of neurons⁵³ has not yet established the extent to which such changes are the nervous system's attempts to preserve a mean firing rate in the face of shifting environmental conditions, that is, homeostasis, or whether the cell's firing behavior is adjusted to optimize information transmission, a more sophisticated behavior. This remains an open topic for future research.

The power and limitations of neurons

The view of neurobiological computation advocated here amounts to the following. Individual nerve cells convert the incoming streams of binary pulses into analog, spatially distributed variables, such as postsynaptic membrane potential and calcium distribution throughout the dendritic tree and cell body. A number of transformations can be applied to these variables besides subtraction and addition: low- and band-pass filtering, normalization, gain control, saturation, amplification, multiplication and thresholding²³. Common to these transformations are simple arithmetic operations (division, multiplication) that are carried out in a feedforward manner, following the predominant signal flow from the dendrites to the spike-initiation zone. If spikes are generated locally in the dendrites, they can be thought of as expressing intermediate results of these global computations in a binary manner. This allows for two levels of nonlinear interactions (first level, local synaptic interactions before dendritic spike initiation; second level, global interactions throughout the dendritic tree) before the sum of all of these interactions is compared against a threshold at the spike-initiating zone.

The final result is sent out to the cell's postsynaptic targets and also backward, into the dendritic tree. Such backpropagating action potentials could support sophisticated Hebbian synaptic memory algorithms or implement coincident detection operations in the 10-ms range. The operating range and sensitivity of these operations are probably adapted to the synaptic input over various time scales.

Although such a neuron is more powerful than its feeble-minded linear threshold relative, it has limitations. For instance, any computation that requires more than two recursive nonlinear interactions would be difficult to implement at the single-cell level. The

MAX operation discussed in this issue by Riesenhuber and Poggio⁵⁴ (computing the maximum of a set of scalar variables) or operations requiring inordinate amount of precision are likely to require a small network of neurons. This still leaves individual neurons with a toolbox of computational primitives that, in conjunction with ubiquitous plastic synapses, dwarf the circuit elements available to the electronic circuit designer today.

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Viewpoint • Models are common; good theories are scarce

I like to draw a distinction between models and theories, and, although the dividing line can be fuzzy, I still think the difference is a real one. Models describe a particular phenomenon or process, and theories deal with a larger range of issues and identify general organizing principles. For example, one might make a model of some aspect of synaptic transmission and use this model to connect observations (fluorescence intensity as a function of time in an imaging experiment, for example) to some mechanistic aspect of synaptic function (such as vesicle recycling). A theory of synaptic transmission, by contrast, would have to account for many properties of synapse function, and relate these properties to principles of information processing. Such a theory might unify models of various forms of short-term plasticity (facilitation, depletion, augmentation and so on) and describe how dynamic filtering characteristics resulting from this plasticity optimize some aspect of information transfer. Models have a long history in neurobiology, from cable theory through the Hodgkin-Huxley equations, and at least some models are recognized as having been essential for the development of our subject. Theories, on the other hand, are scarce, and I cannot think of one that has made a really significant contribution to neurobiology.

Even so, I still believe that theories will be important—indeed vital—for further advances in the field. The reason for this belief is my observation that many areas of biology have progressed pretty much as far as they can by the current techniques of systematically changing one variable at a time to determine what causes what. For example, we have a pretty good idea about what V1 and MT do (although not how the neural circuits do it), but little notion about the function of the other three dozen visual areas. The approach that has been successful for understanding V1 and MT—noticing that certain stimulus properties induce firing of cortical neurons and then systematically characterizing those stimulus properties—may work for a few more visual areas, but I believe the parameter space that must be explored is too large for this approach to be successful for all visual areas. The stimulus parameters needed to describe V1 receptive fields are simple, but we do not even know how to characterize the complex receptive fields in inferotemporal cortex. We will need to develop theories of vision to guide experiments.

The development of theoretical neurobiology will come slowly, though, for at least two reasons. The first is that theory in biology is hard. In physics, everyone knows the important questions (how do you explain high-temperature superconductivity?), and the trick is to get an answer. In biology, however, one must simultaneously figure out the question to ask and how to answer it; this makes things both more difficult and more interesting. A second, related problem is that neurobiology lacks general laws (like the second law of thermodynamics) that can give traction in a problem; in biology, we must not only identify questions, but we need to formulate principles that can serve as the basis for general statements.

In discussions with colleagues, I detect an easing of the hostility toward theory that was common among experimental neurobiologists in the past, and I find a general acceptance of the notion that we must have theory in neurobiology. This atmosphere of acceptance is an essential ingredient for a theoretical neurobiology. Now the theorists must actually produce something of use.

CHARLES F. STEVENS

Molecular Neurobiology Laboratory, The Salk Institute, 10010 N. Torrey Pines Road, La Jolla, California 92037, USA

e-mail: stevens@salk.edu