

# DENDRITIC INTEGRATION OF EXCITATORY SYNAPTIC INPUT

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A fundamental function of nerve cells is the transformation of incoming synaptic information into specific patterns of action potential output. An important component of this transformation is synaptic integration — the combination of voltage deflections produced by a myriad of synaptic inputs into a singular change in membrane potential. There are three basic elements involved in integration: the amplitude of the unitary postsynaptic potential, the manner in which non-simultaneous unitary events add in time (temporal summation), and the addition of unitary events occurring simultaneously in separate regions of the dendritic arbor (spatial summation). This review discusses how passive and active dendritic properties, and the functional characteristics of the synapse, shape these three elements of synaptic integration.

## CABLE FILTERING

Dendrites have been commonly modelled as cables and the flow of current between two points of a dendrite has been usually assumed to decay as a result of filtering along the process.

## HEBBIAN PROCESSES

Plastic processes that require temporal coincidence between incoming synaptic activity and postsynaptic depolarization.

## AXIAL RESISTANCE

The resistance to the flow of ionic current along an axon or a dendrite. Axial resistance decreases as a function of the radius of the process and increases as a function of its length.

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Most neurons of the mammalian central nervous system receive thousands of excitatory and inhibitory synaptic inputs that are widely spread across their intricate dendritic arbors. Whereas synaptic input is broadly distributed, action potential output usually occurs in a more localized region of the proximal axon<sup>1,2</sup>. Because of this spatial arrangement, the distance between the various synaptic inputs and the final integration site can vary to a great degree. The combination of this large variation in synaptic distance and the CABLE FILTERING properties of dendrites can, in theory, cause the amplitude and temporal characteristics of functionally similar inputs to be highly variable at the final integration site<sup>3–8</sup>.

The impact of any given synapse on the neuron firing will depend primarily on the location of the synapse along the dendrite, unless the filtering properties of the dendrites are compensated for by specific mechanisms. This location dependence could be so profound that even the basic elements of synaptic integration would depend on the pattern of spatial input. Furthermore, the distorting effects of the dendritic arbor could prevent a neuron from determining accurately the total incoming synaptic activity, decrease the effectiveness of HEBBIAN PROCESSES and increase the variability of action potential discharge. In consequence, the existence of mechanisms for reducing the dependence of synaptic

effectiveness on input location could have important advantages for neuronal function.

Although theoretical analyses have predicted a clear location-dependent variability of synaptic input, many functional properties of the neuron can actually reduce this variability. They include the passive and active properties of the postsynaptic cell membrane, as well as various pre- and postsynaptic properties of the synapses themselves. In this review, I provide a brief description of the filtering effects of dendrites and how they affect propagation of the excitatory postsynaptic potential (EPSP). Next, I discuss data indicating that, in spite of these filtering effects, the impact of a given synapse may not be strictly dependent on the location of the synapse. The mechanisms believed to be responsible for the reduction of location dependence are examined, before I consider finally the potential consequences of location-independent synaptic input on neuronal function.

## Dendritic filtering

The filtering effects of dendritic arbors have been appreciated for decades. About 40 years ago, Wilfrid Rall began an influential series of studies modelling the passive electrical properties of dendrites using three cable parameters: AXIAL RESISTANCE ( $r_i$ ), MEMBRANE CAPACITANCE ( $C_m$ ) and MEMBRANE CONDUCTANCE ( $G_m$ )<sup>3–5,7</sup>. The flow of

Box 1 | **Theoretical dependence of synaptic input on location**

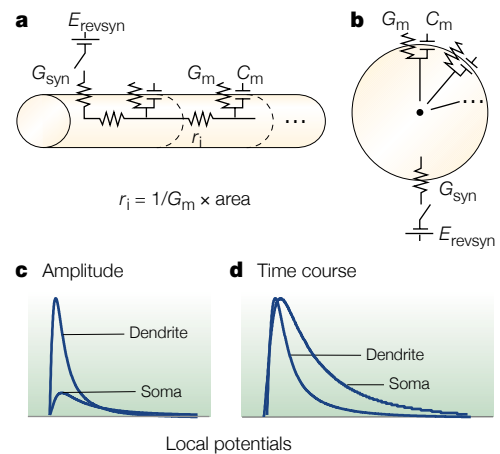
Cell bodies and neuronal processes are commonly modelled as electrical circuits, models that take into account the geometry of the structure being analysed and that make strong predictions about the dependence of current flow on shape. The top panel of the figure shows the equivalent circuit for dendritic cables (Aa) and somatic spheres (Ab) where  $G_m$  and  $C_m$  are the resting conductance and capacitance of a unit of membrane and  $r_i$  is the axial resistance of the intracellular side of a unit of cable. A synapse is represented as a synaptic conductance ( $G_{syn}$ ) in series with the synaptic battery ( $E_{revsyn}$ ). In the case of a dendrite, synaptic current will flow through the membrane into the parallel  $G_m$  and  $C_m$  as well as into the next compartment through  $r_i$ . In contrast, the spherical soma does not have extra pathways for current flow and all synaptic current will flow into the somatic  $G_m$  and  $C_m$ . Similarly, geometry also affects input resistance such that it is inversely proportional to compartment area (Ac). As a result, the local amplitude of an excitatory postsynaptic potential (EPSP) generated by the same synaptic conductance will be larger in the small-diameter, high-resistance dendrite than in the spherical soma. At the same time, the availability of pathways for current flow other than  $G_m$  and  $C_m$  causes synaptic current to flow away from the synaptic compartment (Ad), speeding up the decay of the dendritic EPSP in relation to the soma.

How does this effect of geometry affect synaptic current at different points of the dendritic arbour, such as those schematized in Ba? If the synaptic current (Bb; solid line) is recorded locally in either compartments 6 (left) or 2 (right), it will be identical in both sites. In contrast, the current leaving the synaptic compartment (loss current; dashed line) will not. This observation results from the fact that the proximal region of the dendrite becomes isopotential with the soma much faster than the distal region, reducing the driving force for current flow away from the input site. Because the loss of current is more prolonged in the distal regions, the distal EPSPs are more transient than the proximal ones (Bc) (see REF. 4).

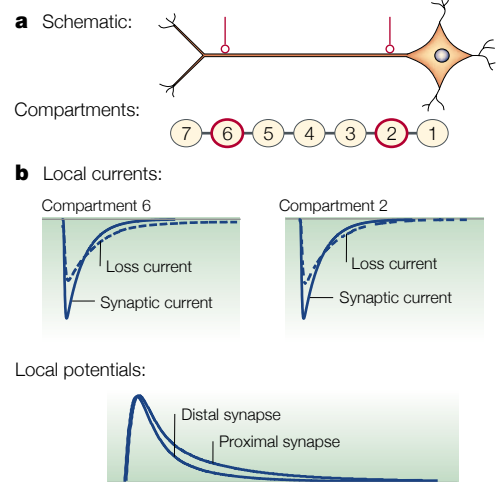
synaptic current into  $G_m$  and  $C_m$  produces a change in the local membrane potential that depends on the neuronal geometry and on these three cable parameters. The axial resistance causes a continuous voltage drop between the site of input and the soma. As a result, the driving force for current flow across  $G_m$  decreases progressively with distance from the cell body. Furthermore, the temporary storage of synaptic charge in  $C_m$  slows the kinetic properties of the resulting change in membrane potential (BOX 1).

Because  $r_i$  increases as a function of length and  $C_m$  increases as a function of membrane area in any given dendrite, distal synapses will experience more amplitude and kinetic filtering than proximal synapses. As a result, distal EPSPs should have smaller amplitudes than proximal synaptic events. In contrast, the increased filtering experienced by distal inputs should have a different effect on the summation of several EPSPs. Dendritic filtering should prolong the time window over which voltage changes caused by other synapses, thereby extending the period over which summation of distal

**A Dendritic versus somatic input**



**B Proximal versus distal dendritic input**



synapses can effectively occur. Therefore, the increased dendritic filtering experienced by distal synaptic inputs should have two distinct effects on their integration properties: it should produce EPSPs of smaller amplitude but, at the same time, longer periods of temporal integration at the soma<sup>3-8</sup> (FIG. 1).

Rall's theoretical analysis predicted that synapses could be functionally distinguished on the basis of dendritic location and that the impact of individual synapses would decrease with distance from the soma. For Rall, the slower, distal EPSP would only cause a subthreshold change in somatic membrane potential, whereas activity from a few of the larger, more transient, proximal synapses would produce sharp, spike-triggering depolarizations<sup>3</sup>. In modern terms, the neuron would operate in a TEMPORAL-INTEGRATION MODE for the distal inputs and in a COINCIDENCE-DETECTION MODE for the proximal inputs<sup>9</sup>. The cable properties of dendrites have therefore been thought to exert a shaping force on the EPSP that, if not countered, could have an important impact on the temporal pattern of action potential output produced by any given spatio-temporal pattern of synaptic input.

**MEMBRANE CAPACITANCE**  
The cell membrane separates and stores electrical charge, thereby producing a relatively large electrical capacitance, which increases as a function of membrane area.

**MEMBRANE CONDUCTANCE**  
The sum of all of the ionic conductances of the membrane. It is the reciprocal of the membrane resistance.

**TEMPORAL-INTEGRATION MODE**  
Firing of action potentials in response to the summation of temporally dispersed synaptic activity. The synaptic input at the soma has small amplitude and long duration.

**COINCIDENCE-DETECTION MODE**  
In this mode, a cell fires action potentials in response to the simultaneous arrival of a small number of usually large amplitude, short duration inputs.

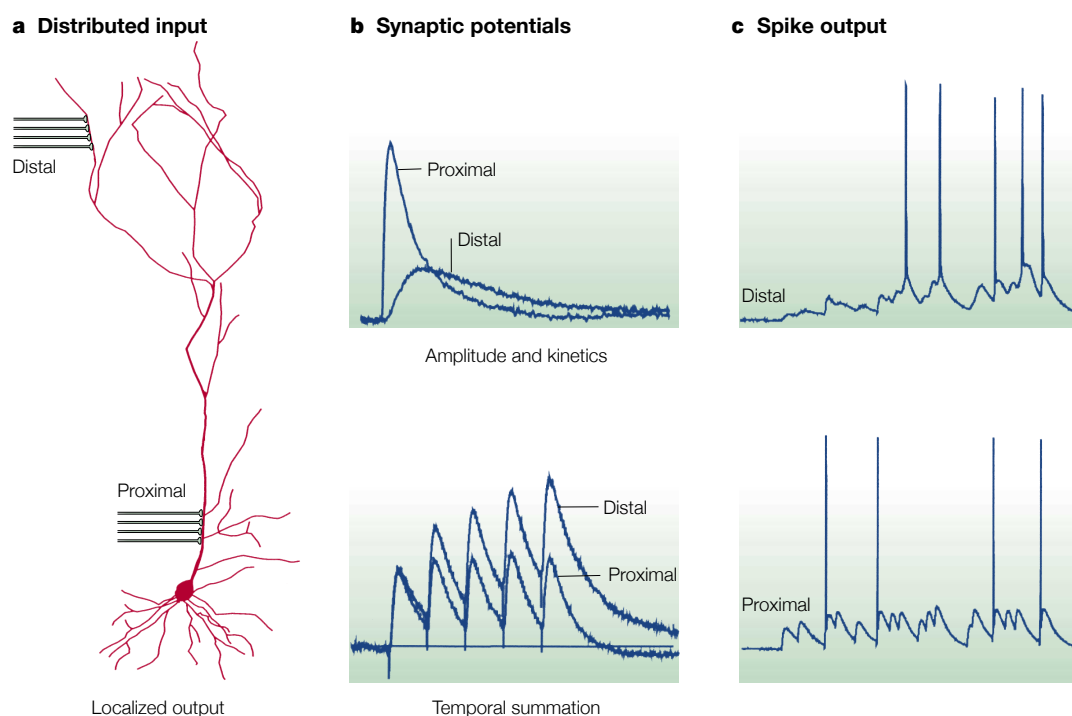


Figure 1 | **The filtering effects of dendrites should be accompanied by location-dependent synaptic integration.**

**a** | A CA1 pyramidal neuron with synaptic input distributed across the dendritic arbor. **b** | Dendritic filtering causes distal inputs to be smaller and slower at the soma. The temporal summation is greater for slower distal events than for the proximal input. **c** | When compared with proximal inputs, the smaller, slower distal inputs should produce a very different action potential output pattern for the same pattern of input. All traces represent somatic membrane potential in response to electrical stimulation (**b**) or excitatory postsynaptic current (EPSC)-shaped current injections (**c**) in the presence of 50  $\mu\text{M}$  ZD7288, a blocker of transient outward current, carried by dendritic hyperpolarization-activated potassium channels ( $I_h$ ).

A series of recent experiments has tested the validity of those theoretical predictions. As I discuss in the following section, most of the evidence obtained so far indicates that, contrary to the theory, synaptic integration is largely independent of input location.

#### Location dependence of synaptic integration

The location dependence of synaptic input has been examined in various cell types, especially in hippocampal CA1 and neocortical pyramidal cells, as well as in spinal motor neurons. In contrast to Rall's predictions, there is now considerable evidence to indicate that, within a single class of inputs, most components of synaptic integration may show minimal dependence on the location of the synapse. This evidence is now examined with an emphasis on data from Schaffer collateral synapses on hippocampal CA1 pyramidal neurons.

**Unitary EPSP amplitude.** In the first examination of the location dependence of synaptic input to CA1 neurons, Andersen *et al.*<sup>10</sup> concluded that proximal and distal Schaffer collateral synapses could elicit similar patterns of action potential firing and found that the shape of the EPSP was relatively independent of synapse location. Subsequently, Redman and colleagues reached a similar conclusion through a statistical analysis of excitatory postsynaptic current (EPSC) fluctuations. This group

obtained evidence that the amplitude of the QUANTAL CURRENT at the soma was independent of the location of the synapse along the dendrite<sup>11</sup>. Nevertheless, previous work in his own laboratory had shown that evoked EPSP amplitude seemed to decrease with distance from the soma because the amplitude of EPSPs evoked by stimulation of single CA3 neurons decreased as the time to reach the peak amplitude increased<sup>12</sup>. To reconcile the data, Redman and colleagues proposed that the QUANTAL CONTENT of evoked Schaffer collateral EPSP decreased with distance from the soma<sup>11</sup>. Subsequent work has shown that the quantal EPSP amplitude of single sensory Ia fibres in spinal motor neurons is location independent<sup>13,14</sup>. More recently, a study using localized release of CAGED GLUTAMATE has shown that the amplitude of the evoked current measured at the soma is independent of the site of glutamate application along the apical dendrite of hippocampal CA1 pyramidal neurons<sup>15</sup>. Similar results have also been reported for pyramidal cells of layer V of the neocortex<sup>16</sup>.

The ability to record synaptic activity from several locations on the same neuron simultaneously has provided the opportunity to test directly many long-standing ideas about the dendritic processing of synaptic information (FIG. 2). Using dual whole-cell patch-clamp recordings in combination with localized MINIMAL STIMULATION TECHNIQUES, it has been found that the amplitude of unitary EPSP at the soma of CA1 pyramidal cells is

#### QUANTAL CURRENT

The current elicited by the transmitter released from a single synaptic vesicle.

#### QUANTAL CONTENT

The number of quanta released per action potential.

#### CAGED GLUTAMATE

An inactive derivative of glutamate that can be transformed into the active transmitter, usually by photolysis of the precursor. It provides an efficient means for the spatially restricted application of glutamate.

#### MINIMAL STIMULATION TECHNIQUES

Methods to elicit transmitter release from a few (ideally one) synaptic contacts.

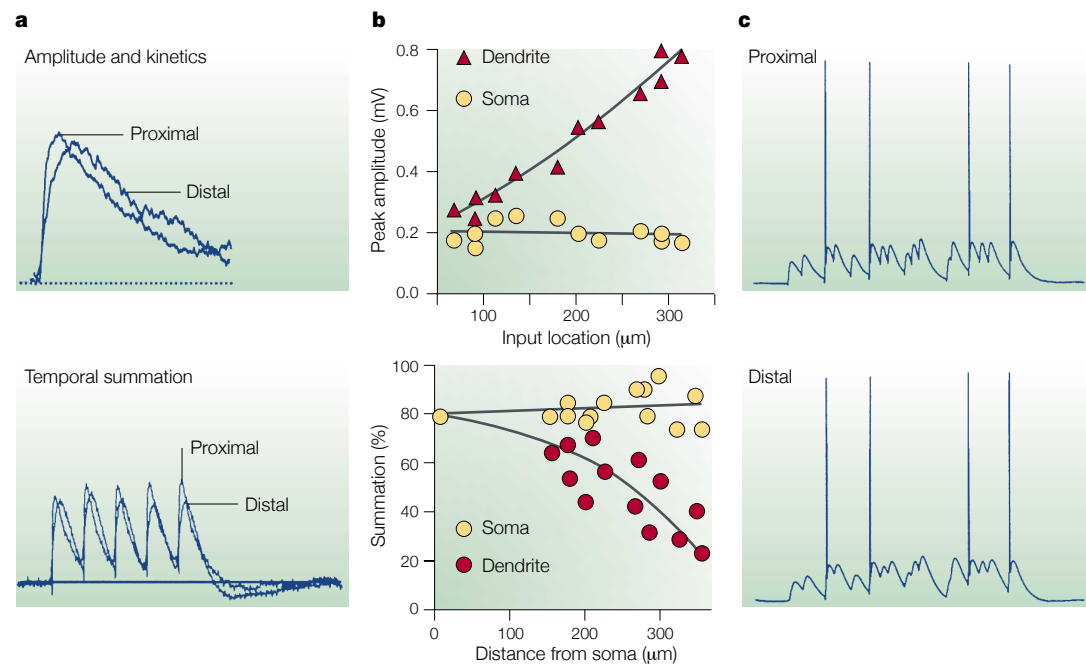


Figure 2 | **Synaptic integration in CA1 pyramidal neurons is independent of location.** **a** | Upper traces: The average unitary excitatory postsynaptic potentials (EPSPs) recorded at the soma of a neuron receiving distal and proximal input. Somatic EPSP amplitude is similar in spite of location differences. Lower traces: The amount of temporal summation at the soma is the same for a 50 Hz train of stimuli applied to distal (~300 μm) or to proximal Schaffer collateral inputs (~50 μm). **b** | Upper plot: Mean EPSP amplitude as a function of input distance from the cell body for recordings made at the soma (yellow circles) or at the dendrite (red triangles). EPSP amplitude at the site of input increases with distance from the soma, whereas somatic amplitude stays relatively constant. Lower plot: temporal summation during a 50 Hz train of stimuli as a function of distance from the cell body for recordings made at the soma (yellow circles) or the dendrite (red circles). The plot shows that summation at the site of input decreases with distance from the soma, whereas somatic summation stays relatively constant. **c** | Somatic voltage in response to current injected through the somatic electrode (proximal) or through the dendritic pipette located about 350 μm away from the soma (distal). The temporal pattern of action potential output is independent of input location. (Figure adapted with permission from *Nature Neurosci.* (REFS 17, 19) © (2000) Macmillan Magazines Ltd.)

independent of synapse location across the entire range of Schaffer collateral inputs<sup>17</sup>. These recordings have also shown that the EPSP amplitude recorded precisely at the dendritic site of input experiences a progressive threefold to fourfold increase as a function of distance from the soma. In other words, if the amplitude of an input is expected to decrease by 20% while propagating to the soma (from 1.0 to 0.8 mV), then the amplitude recorded at the synaptic site will be 25% larger (from 1.0 to 1.25 mV)<sup>17</sup>. If the input is to decay by 70% (from 1.0 to 0.3 mV), then a threefold increase in local amplitude is observed (from 1.0 to 3 mV)<sup>17</sup>. These data have shown that local EPSP amplitude is increased just enough to counterbalance the filtering effects of the dendrite such that all inputs have roughly the same amplitude after propagation to the soma (FIG. 2)<sup>17</sup>.

**EPSP kinetics and temporal summation.** Similar recordings in CA1 pyramidal neurons have shown that, although the rise times of somatic EPSPs show location dependence and increase with distance from the soma, the widths of the EPSPs do not (FIG. 2)<sup>17–21</sup>. As all EPSPs last roughly the same time in these neurons, temporal summation of several EPSPs at the soma is virtually independent of synapse location for a large range of stimulation frequencies (5–100 Hz) and amplitudes

(0.5–5 mV)<sup>19</sup>. A similar location independence of somatic EPSP HALF-WIDTHS and of temporal summation has also been reported for neocortical layer V pyramidal neurons<sup>21</sup>.

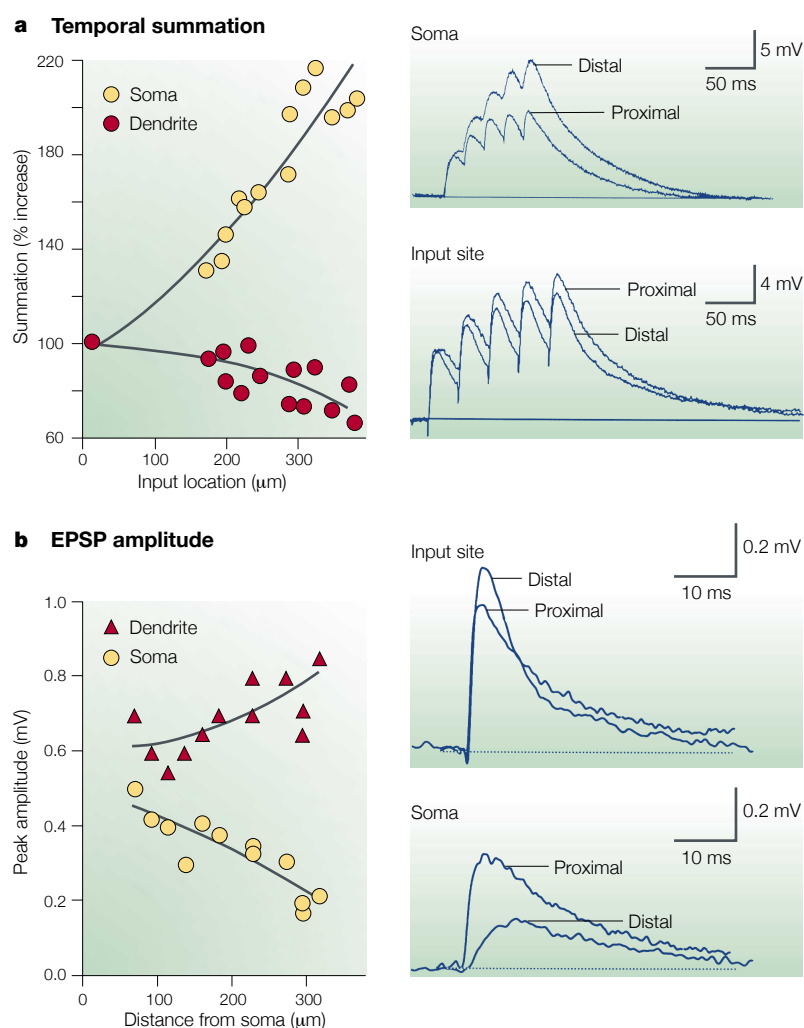
How can the more filtered, distal EPSPs have the same duration as proximal events? As was observed for the normalization of EPSP amplitude, the local dendritic EPSP half-widths and DECAY TIME CONSTANTS progressively decrease with distance from the soma. Again, the local EPSP shape is modified just enough to counterbalance the filtering effects of the dendrite and to greatly reduce the location dependence of EPSP duration and temporal summation<sup>19,21</sup>.

**Spatial summation.** In contrast to unitary EPSP amplitude and temporal summation, a small degree of location dependence has been observed for one aspect of spatial summation in CA1 pyramidal neurons. Using iontophoretically applied glutamate, Cash and Yuste<sup>22</sup> have shown that the summation of two stimuli applied to different points on the apical trunk of the dendrite is smaller than the expected linear sum of the individual events. This sublinearity was evident only for distant inputs and disappeared with repetitive stimulation. Furthermore, the location dependence was seen only for inputs to the apical trunk and not to other parts of the dendritic arbor. Also, the degree of this sublinearity is

**EPSP HALF-WIDTH**  
The duration of an EPSP at the point at which its amplitude is half of the peak value.

**DECAY TIME CONSTANTS**  
The initial decay of an EPSP can usually be fitted by a single-exponential function. The time constant derived from this fit describes how quickly an EPSP decays.





**Figure 3 | EPSC-shaped current injections show that the passive morphology of CA1 pyramidal neurons does not fully counter location-dependent synaptic variability. a |** Temporal summation for a train of 50 Hz excitatory postsynaptic current (EPSC)-shaped current injections measured at the soma or at the dendrite in the presence of ZD7288, a blocker of transient outward current, carried by dendritic hyperpolarization-activated potassium channels ( $I_h$ ). Although the local summation decreases as the input site is moved away from the soma (red symbols and top traces), temporal summation of the propagated excitatory postsynaptic potentials (EPSP) at the soma remains largely dependent on the input location (yellow symbols and bottom traces). This indicates that the passive membrane properties of the cell are not capable of normalizing temporal summation at the soma. **b |** EPSP amplitude at the site of input (red triangles, top traces) or at the soma (yellow circles and bottom traces) for EPSC-shaped current injections. Although the local EPSP amplitude increases with distance, the somatic EPSP amplitude continues to show a large amount of location dependence, indicating that postsynaptic membrane properties cannot normalize unitary EPSP amplitude. (Figure adapted with permission from *Nature Neurosci.* (REFS 17, 19) © (2000) Macmillan Magazines Ltd.)

likely to be voltage dependent, as the summation of smaller unitary depolarizations seems to behave more linearly and to show a reduced location dependence<sup>22</sup> (J.C.M., unpublished observations). Although it is still difficult to draw definitive conclusions from the available data, there does seem to be a small level of location dependence to some aspects of spatial summation in CA1 pyramidal neurons.

In summary, evidence from different cell types is beginning to show that, contrary to theoretical expecta-

tions, the three components of synaptic integration — unitary amplitude, and temporal and spatial summation — show minimal location dependence. What dendritic and synaptic mechanisms are responsible for determining the integration properties and for reducing the variability of the synaptic responses along the apical dendrite in these cells? The different mechanisms can be divided into three general categories: morphological (passive properties of the membrane), active properties of the membrane and synaptic mechanisms. The next sections discuss evidence for the effect of each of these possible mechanisms on the separate components of synaptic integration.

### Neuron morphology

The morphology of the neuron could affect the amplitude and the shape of local EPSPs and potentially counter some aspects of the location dependence of synaptic variability. It has been shown both in multi-compartmental computer models and in dendritic recordings that the local input resistance for a transient event increases, whereas local capacitance decreases, with distance from the soma<sup>17,23–25</sup>. This effect has generally been ascribed to the decrease in compartment size that occurs as the diameter of the distal dendrites decreases progressively<sup>23,24</sup>. The subsequent increase in total  $r_i$  with distance from the soma can also contribute to this effect.

Morphology also determines the ISOPOTENTIALITY of the local dendritic compartments. Dendritic arbors are complex branched structures in which current flows away from and towards the synaptic-input site, and not only into the membrane resistance and capacitance<sup>23–25</sup>. The specific direction of current flow will be determined by the potential differences established between the different regions of the cell. So, the other paths for current flow provided by the dendritic branches dictate that dendrites are less isopotential than the large spherical soma<sup>8,23,24</sup>. What is the impact of these differences on synaptic integration?

**Unitary EPSP amplitude.** The changes in input resistance and capacitance that occur in distal dendritic compartments cause EPSP amplitude at the site of input to increase with distance from the soma, as has been observed on CA1 pyramidal cells<sup>17,23–25</sup>. Although the increase in depolarization is not necessarily proportional to the increase in input resistance, the increase in local EPSP amplitude is substantial and depends on passive parameters as well as on neuron morphology<sup>17,23,24</sup>. In dendritic recordings, EPSC-shaped current injections cause voltage deflections that also increase in amplitude with distance from the soma (~50% by 325  $\mu\text{m}$ ; FIG. 3)<sup>17</sup>. The amount of increase, however, is notably smaller than that observed in theoretical models and, more importantly, it is much smaller than that shown for the actual unitary synaptic input. Accordingly, and in contrast to that observed for synaptic inputs, these EPSC-shaped current injections into the dendrite show a sharp location dependence, as their amplitude decreases for the more distal injection sites (FIG. 3)<sup>17,23,24</sup>. Therefore, it seems that the increase in local dendritic input resistance

**ISOPOTENTIALITY**  
The degree to which the dendritic compartments are all at the same potential.

contributes only slightly to the increases in local EPSP amplitude that are responsible for normalizing the EPSP amplitude at the soma<sup>23–25</sup>.

**EPSP kinetics and temporal summation.** The changes in compartment size and branching that occur with distance from the soma can also shape the kinetics of the local EPSPs. As mentioned above, the spread of current throughout the dendrites is sufficient to cause an initially faster decay of synaptic depolarization in the dendritic compartment than in the soma. This effect is related to the proximity of the synaptic input to the cell body; more distal inputs show the fastest initial decay phase<sup>4,17,21,23–25</sup>. However, once the cell becomes isopotential, the decay of the EPSP would be the same at every point.

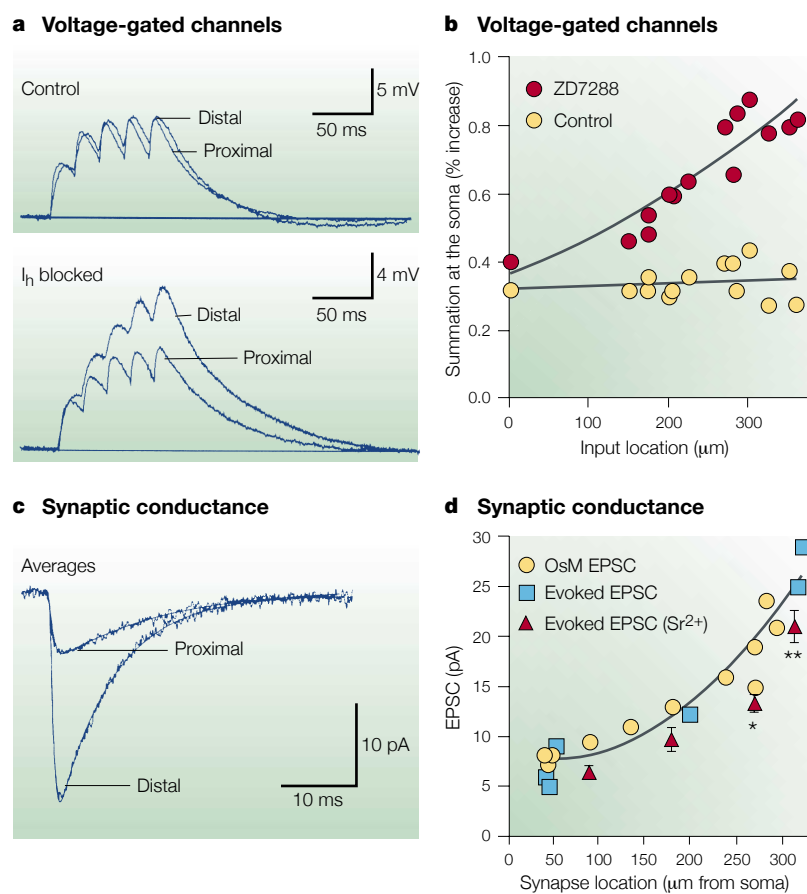
In conclusion, as has been observed for the local EPSP amplitude, EPSP half-width and local temporal summation do decrease progressively with distance from the soma as a consequence of neuron morphology (FIG. 3)<sup>4,17,23,24</sup>. However, as was also the case for the EPSP amplitude, the impact of the passive structure on the time course and summation of the synaptic potential is not adequate to completely counteract the filtering effects of the dendrite<sup>17,21</sup>. Therefore, other mechanisms besides the passive properties of the dendrites are required to reduce the effect of filtering by an extra factor of two or three. So, whereas the dendritic morphology of pyramidal neurons can contribute to spatial gradients that affect synaptic integration, it is unlikely that passive geometry alone can substantially reduce the location-dependent variability of synaptic inputs<sup>23–25</sup>. Although this idea has been confirmed in neurons such as CA1 and neocortical pyramidal cells, the possibility remains that the different morphology of other cell types, such as dentate granule cells, CA3 pyramidal neurons and CA3 interneurons, could be more important in normalizing EPSP amplitude<sup>25</sup>.

**Spatial summation.** The larger, local EPSPs produced by the higher input resistance of the distal dendrites will experience reduced driving forces for synaptic current flow compared with more proximal synaptic events<sup>22–24</sup>. This effect could potentially induce a moderate location dependence of the EPSP at the soma during the spatial summation of inputs. In this case, a greater sublinear summation should be seen for distal versus proximal inputs and, indeed, such location dependence has been observed for distal inputs to the apical trunk of CA1 pyramidal neurons<sup>22</sup>. However, the sublinearity of this input was smaller than expected and was not present for other input locations. These results, along with pharmacological data that will be discussed below, have led to the belief that the impact of the passive structure of the dendrites is overwhelmed by other mechanisms such as the opening of dendritic voltage-gated ion channels<sup>22</sup>. In fact, this conclusion is representative of the impact of pyramidal cell morphology on most aspects of synaptic integration. Whereas the passive structure of the dendrites does indeed have an important impact on integration, this impact is limited in comparison with other mechanisms in the dendrites, as will be discussed in the next section.

### Active properties of dendrites

Voltage-gated ion channels have been found in the dendrites of virtually every mammalian neuron studied so far, although their exact subcellular distribution is specific for each cell type (for a review, see REF. 26). The currents carried by these channels are important in shaping the integrative properties of neurons. For instance, the inward currents through Na<sup>+</sup> and Ca<sup>2+</sup> channels could provide extra ion flux to replace the synaptic current lost across the membrane resistance. The combination of an initial inward current followed by a transient outward current, carried by dendritic hyperpolarization-activated K<sup>+</sup> channels ( $I_h$ ), could also reduce the filtering effects of the dendritic capacitance by charging and discharging the membrane during the EPSP<sup>27–29</sup>. Indeed, there have been many reports on the capability of voltage-gated ion channels to shape both single and repetitive excitatory synaptic input in hippocampal and neocortical pyramidal neurons<sup>28–37</sup>. Furthermore, the voltage-gated ion channels present in dendrites allow action potentials initiated at the axon to propagate back into the dendrites, where they can then sum with incoming synaptic activity<sup>2,26</sup>. This summation tends to increase the amplitude of the back propagating spikes and has been reported to lead to the generation of Ca<sup>2+</sup>-mediated potentials in some cells<sup>38,39</sup>. This dendritic electrogenesis can greatly enhance the impact of very distal synaptic input such as that received by the apical tufts of layer V neocortical pyramidal cells<sup>39,40</sup>. In summary, the function of active channels in shaping EPSP integration will depend on the precise channel distribution and on the neuronal geometry of any particular cell. Nevertheless, some general principles have emerged for pyramidal neurons, as discussed below.

**Unitary EPSP amplitude.** In CA1 neurons<sup>26</sup> and in neocortical pyramidal cells<sup>28,41</sup>, the impact of the outward currents tends to increase with distance from the soma because the density of transient K<sup>+</sup> and  $I_h$  channels increases along the length of the apical dendrites. As a consequence, the main impact of dendritic ion channels on unitary synaptic input should not be a boosting of the distal synaptic amplitude. Instead, the channels should increase the location dependence of somatic EPSP amplitude by reducing distal EPSPs even more than proximal ones. However, for these channels to actually participate in shaping synaptic inputs, the amplitude of the EPSPs needs to be sufficient to activate a substantial fraction of the channels in question. For instance, assuming a resting potential of  $-70$  mV, the depolarization should be roughly 10–15 mV for the activation of Na<sup>+</sup> and low-voltage-activated Ca<sup>2+</sup> channels, and 15–20 mV for the opening of A-type K<sup>+</sup> channels<sup>26</sup>.  $I_h$  is active at rest but the deactivation rate of these channels is so slow that current through this channel population will mostly affect only the EPSP decay and not the amplitude<sup>18,19,21</sup>. Therefore, although the exact effect of voltage-gated ion channels on unitary EPSP amplitude has yet to be determined, their effect on these small amplitude events should be limited<sup>17</sup>. On the other hand, summed EPSPs will be larger in amplitude and therefore shaped to a larger degree by dendritic ion channels.



**Figure 4 | Other mechanisms such as active membrane and synaptic properties are required to completely counter location-dependent synaptic variability.** **a** | Membrane voltage recorded at the soma in response to a train of five excitatory postsynaptic current (EPSC)-shaped current injections delivered at 50 Hz through the dendritic or the somatic pipette. Upper traces were obtained under control conditions and lower traces were obtained under blockade of transient outward current, carried by dendritic hyperpolarization-activated potassium channels ( $I_h$ ) (20  $\mu$ M ZD7288). Summation at the soma is larger for dendritic current injections but it does not change notably for somatic injections. **b** | Excitatory postsynaptic potentials (EPSP) summation at the soma plotted as a function of the dendritic site of current injection under control conditions (yellow circles) or in the presence of ZD7288 (red circles). When  $I_h$  is blocked, the amount of summation at the soma increases as input location is moved away. **c** | Average of EPSC, evoked by the localized application of a solution of high osmolarity, and recorded from a proximal (~100  $\mu$ m) and a distal (~280  $\mu$ m) site in the apical dendrite of two different neurons. **d** | Plot of mean EPSC amplitude as a function of input distance from the soma for EPSCs evoked by high osmolarity (yellow circles) or by electrical stimulation in normal (blue squares) or  $Sr^{2+}$ -containing extracellular solution (red triangles).  $Sr^{2+}$  causes desynchronized release of transmitter and provides a better estimate of the amplitude of the unitary synaptic response. (Figure adapted with permission from *Nature Neurosci.* (REFS 17, 19) © (2000) Macmillan Magazines Ltd.)

**EPSP kinetics and temporal summation.** The impact of dendritic channels on EPSP shape and summation has been studied in pyramidal cells in some detail. For short time intervals (0–5 ms), the summation of two inputs closely spaced in time seems to be linear or slightly supralinear<sup>22,34,35,37</sup>, whereas EPSP summation over longer intervals (5–100 ms) has been reported to be sublinear<sup>19,35,37</sup>. This nonlinear behaviour is affected by blockade of voltage-dependent channels. For example, blockade of  $Na^+$ ,  $Ca^{2+}$  or NMDA receptor channels decreases or abolishes the supralinearity, whereas  $I_h$  and  $K^+$  channel blockade eliminates the sublinear summation<sup>21,22,34,35,37</sup>. Large synchronous synaptic activity

(>30 mV) can initiate dendritic  $Na^+$  spikes that usually do not propagate as action potentials to the soma<sup>19,42</sup>. The ability of a given synaptic input to sum supralinearly is enhanced by repetitive activity, so that large EPSPs occurring later in a train have an enhanced amplitude and are more likely to initiate dendritic spikes<sup>19,22,27,42</sup>. In CA1 pyramidal neurons, this is presumably related to the inactivation of voltage-gated channels (probably A-type  $K^+$  channels) during the train of activity. Therefore, it seems that although dendritic voltage-gated channels may have a limited impact on the amplitude of unitary synaptic input, they actively shape repetitive synaptic potentials of larger amplitude.

Furthermore, the increased density of  $I_h$  channels, found in both CA1 and neocortical pyramidal cells, is prominent in reducing the location dependence of the EPSP half-width and temporal summation<sup>18,19,21,28,32</sup>. The effectively outward active current generated by  $I_h$  channel deactivation during synaptic activity produces a hyperpolarization that tends to shorten the duration of local EPSPs and to counter any local temporal summation during repetitive stimuli<sup>19,21</sup>. As the channel density increases with distance from the soma, the size of the outward current generated at the site of the input also increases, producing the spatial gradient of local EPSP duration and summation described above. Because selective blockade of  $I_h$  channels causes a profound location-dependent synaptic variability, the current generated by  $I_h$  channel deactivation is presumably the most important factor in normalizing temporal summation in CA1 pyramidal neurons (FIG. 4a, b)<sup>19,21</sup>.

**Spatial summation.** A-type  $K^+$  channels present in dendrites seem to be important in shaping spatial EPSP summation in hippocampal pyramidal neurons<sup>22,27,33,35,37</sup>. These channels are prominent in the distal dendritic regions of CA1 and perhaps of other pyramidal cells, where they seem to limit the summation of closely timed distal inputs<sup>22,35,37</sup>. In fact, the location dependence of the sublinear summation described above for CA1 cells is sensitive both to the A-type  $K^+$ -channel blocker 4-aminopyridine and to stimuli that inactivate this class of channel<sup>22</sup>. In CA1 cells, blockade of  $Na^+$  and  $Ca^{2+}$  channels causes sublinear spatial summation in radial oblique dendrites, whereas only tetrodotoxin, a blocker of  $Na^+$  channels, has the same effect on input to basal dendrites. These data indicate that, at least in CA1 cells, there is an interaction between the active conductances present in the dendrites, which linearizes spatial summation in most of the proximal dendritic arbor<sup>22,33</sup>. In CA3 pyramidal neurons, the summation of distal and proximal input is sublinear even under control conditions. This sublinearity is removed by blocking A-type  $K^+$ -channels, but is not affected by  $Na^+$  or  $Ca^{2+}$  channel blockade.

Finally, the integration of synaptic activity with back propagating action potentials provides a unique form of interaction between synaptic inputs at different sites of the dendritic arbor. As reported for layer V neocortical pyramidal cells, any distal input arriving within 10 ms

of other suprathreshold inputs will receive a pronounced boost from the further activation of distal dendritic voltage-gated Na<sup>+</sup> and Ca<sup>2+</sup> channels<sup>39</sup>. Therefore, although the direct interaction between the widely spaced EPSPs is small, the action potential produced by suprathreshold proximal inputs will effectively sum with the incoming distal input to produce a nonlinear form of integration. Furthermore, this interaction should also show some frequency dependence because the probability of initiating Ca<sup>2+</sup>-mediated potentials in the distal apical dendrite increases with repetitive activity for a critical range of frequencies that depends on the cell (60–200 Hz)<sup>39,40</sup>. So, it seems that the active properties of dendrites endow neurons with the ability to produce both linear (spatially normalized summation) and highly nonlinear interactions (local dendritic spiking) between synaptic inputs. The exact effect will depend on the specific spatio-temporal characteristics of the input.

### Synaptic properties

By modifying the size and the kinetic properties of the synaptic conductance, the synapse itself can equip the neuron with a plethora of potential mechanisms to shape synaptic integration. These mechanisms can be presynaptic (such as the vesicular content of transmitter, the number of vesicles released per site, or the number of release sites per terminal) or postsynaptic (receptor number, density, affinity or single-channel conductance and kinetics).

**Unitary EPSP amplitude.** As discussed above, the morphology and active properties of CA1 pyramidal neurons are not likely to confer the level of location independence that has been observed for unitary EPSP amplitude in these cells. Therefore, the dendritic mechanisms for reducing location-dependent amplitude variability are likely to be present at the synapse itself. In support of this idea, the local EPSC amplitude in CA1 pyramidal neurons measured under whole-cell voltage clamp at the dendritic site of input was observed to increase roughly threefold across the range of the Schaffer collateral input<sup>11,17</sup> (FIG. 4c, d). The voltage-clamp of these synapses is good but imperfect (>90% voltage attenuation)<sup>17</sup>. Therefore, the passive properties of the dendrites can have a small impact on the measured EPSC amplitude and kinetics. Because of this, the TIME INTEGRAL of the EPSCs has been used as a more accurate filter-independent measure of synaptic conductance<sup>8,23</sup> and has been found to increase more than twofold across the same range of inputs<sup>17</sup>. These data indicate that unitary synaptic conductance increases with distance from the soma in CA1 pyramidal neurons<sup>11,17</sup> and that this increase is the primary mechanism for reducing the location dependence of unitary EPSP amplitude.

The exact synaptic modification responsible for this increase in conductance is unknown at present. Analysis of EPSC rise times and amplitude distributions indicate that the most plausible candidates might be increases in the number of release sites per terminal and/or increases

in the postsynaptic area and number of glutamate receptors<sup>17,43–49</sup>. Analogous changes in these synaptic parameters have been previously observed in goldfish MAUTHNER CELL dendrites, where the number of release sites per bouton as well as the total area of the active zones are increased in the more distal dendrites<sup>49</sup>. These data are also consistent with the increased sensitivity to glutamate observed in the distal apical dendrites of both neocortical and hippocampal pyramidal neurons<sup>15,16</sup>. So, it seems that several cell types have used an increase in local synaptic conductance to counterbalance the amplitude filtering effects of their dendrites.

The time course of a synaptic event can also affect the level of dendritic filtering notably and, as a consequence, the degree of location dependence of the synaptic input. In the case of glutamate-mediated transmission,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor-mediated events have kinetic properties about one order of magnitude faster than NMDA (N-methyl-D-aspartate) receptor-mediated EPSPs<sup>50</sup>. Because the amount of charge stored in the dendritic capacitance is directly proportional to the rate of change of the membrane potential, the amount of filtering done by a dendritic arbor will depend on the kinetic features of the potential change<sup>8,23,24</sup>. As a result, the faster AMPA-mediated EPSP will experience a greater amount of amplitude attenuation when compared with the slower NMDA-mediated events. Therefore, distal synapses could increase their impact by raising their NMDA-to-AMPA receptor ratio and, in fact, there is some evidence that perforant path synapses in the most distal regions of CA1 pyramidal neurons may use this strategy<sup>51</sup>.

**EPSP kinetics, temporal and spatial summation.** There are some clear examples of how receptor kinetics affect EPSC duration and temporal integration in hippocampal dentate gyrus basket cells and in neurons from brainstem auditory nuclei<sup>52,53</sup>. The AMPA receptor deactivation rates in both of these cell types are rapid (time constant of deactivation = 1.0 ms at 22 °C) and match the EPSC decay times tightly. The extremely rapid time course of synaptic conductance (<0.1 ms at physiological temperature), in conjunction with the fast MEMBRANE TIME CONSTANTS, determines that EPSPs generated by activation of these synapses have a short duration. Rapidly decaying EPSPs show little temporal summation, allowing these cells to function as coincidence detectors, which ensure that the timing of action potential firing is constant from one cell to another in these circuits.

This mechanism could theoretically be used to eliminate the location dependence of temporal summation in other neurons. A differential distribution of AMPA receptors could be present in dendrites such that receptor subunits or splice variants showing rapid deactivation (for example, FLOP VARIANTS of GluR2 or 4) would be predominately located at more distal synapses. In cells that use a change in receptor kinetics to reduce location dependence, an increasing density of I<sub>h</sub> channels would not be required to normalize temporal summation spatially as long as the membrane time constant is homogeneous throughout the neuron.

#### TIME INTEGRAL

By accounting for the charge stored in the capacitance of the cells, the time integral of the EPSC relates more to the steady-state voltage attenuation and is therefore much less affected by dendritic filtering.

#### MAUTHNER CELLS

A bilateral pair of brainstem neurons that receive acoustic information and trigger an escape response characteristic of fish.

#### MEMBRANE TIME CONSTANTS

These describe the time course of voltage changes in neurons. A small time constant means that the membrane potential can change rapidly.

#### FLOP VARIANT OF AMPA RECEPTORS

Two splice variants known as flop and flopp have been characterized. They differ in their response to glutamate, their distribution and their developmental expression.



Whereas such a mechanism is possible, it does not seem to be required in CA1 or in neocortical pyramidal neurons. In these cells, the location-dependent changes observed in local EPSP decay kinetics and summation can be completely reproduced by the dendritic injection of EPSC-shaped currents<sup>17,21</sup>. This strongly indicates that a synaptic modification may not be required for the normalization of temporal summation in these cells because an alteration of dendritic membrane properties is able to complete the task. However, this observation does not completely rule out the possibility that distal glutamate receptors desensitize or deactivate differently from proximal receptors. More studies using rapid application techniques are required to compare the kinetics of synaptic glutamate receptors among the different regions of the dendrites, particularly for the more distal synaptic inputs.

#### Functional impact of location independence

There seem to be several functional benefits associated with eliminating or reducing location-dependent synaptic variability. The normalization of synaptic integration allows a neuron to use Hebbian synaptic mechanisms to store information and it allows this information to be encoded in the temporal firing pattern of a neuronal network. Furthermore, the mechanisms that produce this normalized integration should enrich the repertoire of information processing modes that can be observed in a single neuron.

*Hebbian plasticity.* When unitary EPSP amplitude and spatio-temporal summation are similar among a group of synapses, each input is equally capable of evoking an action potential. In pyramidal cells, this is the case even at the site of input, because the threshold for action potential initiation increases with distance from the soma at a rate remarkably similar to the increase of the local EPSP amplitude<sup>2,17,33</sup>. As a result, the primary determinant of the weight of a synapse would be its history (whether or not it was associated with the elicitation of an action potential) and not its location in the dendrite. In addition, the generation of action potentials is important for the induction of long-term changes in synaptic strength. Therefore, if all synapses are equally capable of firing the postsynaptic cell, all synapses will have a similar probability of inducing enduring changes of synaptic efficacy such as long-term potentiation or long-term depression. Indeed, when location-dependent synaptic variability is reduced, Hebbian mechanisms can store information efficiently in realistic neuronal networks<sup>54</sup>. If, on the other hand, synapse location were the primary determinant of synaptic efficacy, then changing the weight of a synapse as a function of its association with action potential output would become less efficient for storing information<sup>54</sup>. Therefore, reducing location dependence from synaptic weight can have an extremely positive impact on information storage in neuronal networks.

#### Links

ENCYCLOPEDIA OF LIFE SCIENCES Dendrites

*Population synchrony.* The axon of a single CA3 cell can synapse onto the distal dendrites of one CA1 cell and form more proximal synapses on another<sup>45</sup>. Therefore, the spatial innervation pattern of a CA1 pyramidal neuron by any given group of CA3 pyramidal neurons can vary from cell to cell. If the temporal pattern of action potential output from CA1 cells were dependent on the spatial input pattern, it would be difficult to produce synchronous firing from a population of CA1 pyramidal neurons because each cell would receive a spatially different pattern of input. By reducing the location dependence of synaptic integration, a population of CA1 cells that receives widely different spatial patterns of input but similar temporal patterns will fire in synchrony<sup>19</sup>. This synchrony is thought to be an important factor for many functional properties of hippocampal and other neuronal types<sup>55,56</sup>.

*Integration modes.* There are many examples of linear encoding and integration in various sensory systems throughout the brain<sup>57–60</sup>. The reduction of location-dependent synaptic variability and the small amplitude of unitary events could provide a mechanism for the linear summation of activity, where all inputs would contribute equally to the output of the cell. This is, however, only half of the story because ion channels susceptible to modulation (A-type K<sup>+</sup>-channels,  $I_h$ , AMPA receptors and others) are also responsible for the normalization of synaptic weight. In addition, the release of common neuromodulators, such as acetylcholine, noradrenaline and serotonin, at localized regions of the dendrite could lower the firing threshold and alter temporal summation. Furthermore, input patterns are not always highly distributed. So, the appropriate spatio-temporal input pattern in the presence of channel modulation could easily produce a nonlinear form of integration<sup>61–63</sup>, perhaps resulting in the local initiation of dendritic spikes<sup>19,33,42</sup>. The same neuron is therefore able to integrate synaptic inputs in an essentially linear or in a highly nonlinear fashion depending on the type of stimuli that it receives. By removing the location dependence of synaptic input, the neuron has extended the range of possible synaptic integration in the same dendritic arbor from a global, uniform type of processing to one that can be regional and highly nonlinear. Furthermore, this feat has been achieved without compromising the ability of the cells to use mechanisms for associative synaptic plasticity and to fire as a synchronous population.

In conclusion, it seems that CA1 pyramidal neurons and probably other nerve cells have normalized the impact of their synaptic inputs through an intricate interplay between morphology, voltage-gated ion channels and the properties of the synapses themselves. Although each of these features shows an amazing complexity, their interplay has, by reducing dendritic distortion, simplified the information carried by tens of thousands of highly distributed dendritic synapses. This simplification can have powerful consequences for the functional capabilities of neurons.

1. Colbert, C. & Johnston, D. Axonal action-potential initiation and Na<sup>+</sup> channel densities in the soma and axon initial segment of subicular pyramidal neurons. *J. Neurosci.* **16**, 6676–6686 (1996).
  2. Stuart, G., Spruston, N., Sakmann, B. & Häusser, M. Action potential initiation and backpropagation in neurons of the mammalian CNS. *Trends Neurosci.* **20**, 125–131 (1997).
  3. Rall, W. in *Neural Theory and Modeling* (ed. Reiss, R. F.) 5–30 (Stanford Univ. Press, Palo Alto, 1964).
  4. Rall, W. Distinguishing theoretical synaptic potentials computed for different soma-dendritic distributions of synaptic input. *J. Neurophysiol.* **30**, 1138–1168 (1967).
  5. Rall, W., Burke, R. E., Smith, T. G., Nelson, P. G. & Frank, K. Dendritic location of synapses and possible mechanisms for the monosynaptic EPSP in motoneurons. *J. Neurophysiol.* **30**, 1169–1193 (1967).
  6. Mainen, Z. F., Carnevale, N. T., Zador, A. M., Claiborne, B. J. & Brown, T. H. Electrotonic architecture of hippocampal CA1 pyramidal neurons based on three-dimensional reconstruction. *J. Neurophysiol.* **76**, 1904–1923 (1996).
  7. Rall, W. in *Handbook of Physiology. The Nervous System. Cellular Biology of Neurons* Section 1, Vol 1, (eds Kandel, E. R., Brookhart, J. M. & Mountcastle, V. B.) 39–97 (American Physiological Society, Bethesda, 1977).
  8. Jack, J. J. B., Noble, D. & Tsien, R. W. in *Electric Current Flow in Excitable Cells* 125–132 (Oxford Univ. Press, London, 1975).
  9. Segev, I. in *The Theoretical Foundation of Dendritic Function* (eds Segev, I., Rinzel, J. & Shepard, G. M.) 117–121 (MIT Press, Cambridge, Massachusetts, 1995).
  10. Andersen, P., Silvenius, H., Sundberg, S. H. & Sveen, O. A comparison of distal and proximal dendrite synapses on CA1 pyramids in guinea pig hippocampal slices *in vitro*. *J. Physiol. (Lond.)* **307**, 273–299 (1980).
  11. Stricker, C., Field, A. C. & Redman, S. J. Statistical analysis of amplitude fluctuations in EPSCs evoked in rat CA1 pyramidal neurones *in vitro*. *J. Physiol. (Lond.)* **490**, 419–441 (1996).
  12. Sayer, R. J., Friedlander, M. J. & Redman, S. J. The time course and amplitude of EPSPs evoked at synapses between pairs of CA3/CA1 neurons in the hippocampal slice. *J. Neurosci.* **10**, 826–836 (1990).
  13. Jack, J. J., Redman, S. J. & Wong, K. The components of synaptic potentials evoked in cat spinal motoneurons by impulses in single group Ia afferents. *J. Physiol. (Lond.)* **321**, 65–96 (1981).
  14. Inasek, R. & Redman, S. J. The amplitude, time course and charge of unitary excitatory post-synaptic potentials evoked in spinal motoneurone dendrites. *J. Physiol. (Lond.)* **234**, 665–688 (1973).
- Provides one of the first and most convincing demonstrations that the location dependence of synaptic amplitude can be reduced by increasing distal synaptic conductance. They have also used sophisticated analysis techniques to reach the same conclusions on the Schaffer collaterals (reference 11).**
15. Pettit, D. L. & Augustine, G. J. Distribution of functional glutamate and GABA receptors on hippocampal pyramidal cells and interneurons. *J. Neurophysiol.* **84**, 28–38 (2000).
  16. Frick, A., Ziegelgansberger, W. & Dodt, H. U. The subcellular distribution of glutamate receptors in layer V pyramidal neurons. *Soc. Neurosci. Abstr.* **24**, 325 (1998).
  17. Magee, J. C. & Cook, E. P. Synaptic weight is independent of synapse location in CA1 pyramidal neurons. *Nature Neurosci.* **3**, 895–903 (2000).
  18. Magee, J. C. Dendritic hyperpolarization-activated currents modify the integrative properties of hippocampal CA1 pyramidal neurons. *J. Neurosci.* **18**, 7613–7624 (1998).
  19. Magee, J. C. Dendritic I<sub>h</sub> normalizes temporal summation in hippocampal CA1 neurons. *Nature Neurosci.* **2**, 508–514 (1999).
- This paper, followed by reference 17, showed that the location of a synapse has less impact on the amplitude and temporal summation of excitatory postsynaptic potentials (EPSPs) at the soma than expected from theoretical considerations. The location dependence of temporal summation seems to be reduced by the active properties of the dendrites, whereas amplitude seems to be normalized by alterations of synaptic conductance.**
20. Andreasen, M. & Lambert, J. D. C. Factors determining the efficacy of distal excitatory synapses in rat hippocampal CA1 pyramidal neurones. *J. Physiol. (Lond.)* **507**, 421–441 (1998).
  21. Williams, S. & Stuart, G. Site independence of EPSP time course is mediated by dendritic I<sub>h</sub> in neocortical neurons. *J. Neurophysiol.* **83**, 3177–3182 (2000).
  22. Cash, S. & Yuste, R. Linear summation of excitatory inputs by CA1 pyramidal neurons. *Neuron* **22**, 383–394 (1999).
- Probably the most thorough investigation of spatial summation in a central neuron. The authors compared the summation of iontophoretic potentials at different regions of CA1 neurons and found that summation was mostly linear to slightly sublinear in most dendritic regions. The summation was sensitive to blockade of various ion channels and to the temporal pattern of input, leading the authors to believe that an interaction among voltage-gated ion channels linearizes spatial summation.**
23. Rall, W. & Rinzel, J. Branch input resistance and steady attenuation for input to one branch of a dendritic neuron model. *Biophys. J.* **13**, 648–688 (1973).
  24. Rinzel, J. & Rall, W. Transient response in a dendritic neuron model for current injected at one branch. *Biophys. J.* **14**, 759–790 (1974).
- References 23 and 24 provided new insights into the spread of voltage transients in passive arbours. They describe how the structure of the distal dendritic arbour will increase the local input resistance and provide further paths for current flow. These papers convincingly showed how the local passive properties of the dendrites can produce large-amplitude, kinetically brief local dendritic EPSPs but cannot, however, produce larger or faster EPSPs at the soma.**
25. Jaffe, D. B. & Carnevale, N. T. Passive normalization of synaptic integration influenced by dendritic architecture. *J. Neurophysiol.* **82**, 3268–3285, (1999).
  26. Magee, J. C. in *Dendrites* (eds Stuart, G., Spruston, N. & Häusser, M.) 139–160 (Oxford Univ. Press, London, 1999).
  27. Wilson, C. J. Dynamic modification of dendritic cable properties and synaptic transmission by voltage-gated potassium channels. *J. Comput. Neurosci.* **2**, 91–115 (1995).
  28. Stuart, G. & Spruston, N. Determinants of voltage attenuation in neocortical pyramidal neuron dendrites. *J. Neurosci.* **18**, 3501–3510 (1998).
  29. Cook, E. P. & Johnston, D. Voltage-dependent properties of dendrites that eliminate location-dependent variability of synaptic input. *J. Neurophysiol.* **81**, 535–543 (1999).
  30. Gillissen, T. & Alzheimer, C. Amplification of EPSPs by low Ni<sup>2+</sup>- and amiloride-sensitive Ca<sup>2+</sup> channels in apical dendrites of rat CA1 pyramidal neurons. *J. Neurophysiol.* **77**, 1639–1643 (1997).
  31. Lipowsky, R., Gillissen, T. & Alzheimer, C. Dendritic Na<sup>+</sup> channels amplify EPSPs in hippocampal CA1 pyramidal cells. *J. Neurophysiol.* **76**, 2181–2191 (1996).
  32. Nicoll, A., Larkman, A. & Blakemore, C. Modulation of EPSP shape and efficacy by intrinsic membrane conductances in rat neocortical pyramidal neurons *in vitro*. *J. Physiol. (Lond.)* **463**, 693–705 (1993).
  33. Hoffman, D. A., Magee, J. C., Colbert, C. M. & Johnston, D. K<sup>+</sup> channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons. *Nature* **387**, 869–875 (1997).
  34. Schiller, J., Major, G., Koester, H. J. & Schiller, Y. NMDA spikes in basal dendrites of cortical pyramidal neurons. *Nature* **404**, 285–289 (2000).
  35. Urban, N. N. & Barrionuevo, G. Active summation of excitatory postsynaptic potentials in hippocampal CA3 pyramidal neurons. *Proc. Natl Acad. Sci. USA* **95**, 11450–11455 (1998).
  36. Deisz, R. A., Fortin, G. & Ziegelgansberger, W. Voltage dependence of excitatory postsynaptic potentials of rat neocortical neurons. *J. Neurophysiol.* **65**, 371–382 (1991).
  37. Margulis, M. & Tang, C. Temporal integration can readily switch between sublinear and supralinear summation. *J. Neurophysiol.* **79**, 2809–2813 (1998).
  38. Magee, J. C. & Johnston, D. A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science* **275**, 209–213 (1997).
  39. Larkum, M. E., Zhu, J. J. & Sakmann, B. A new cellular mechanism for coupling inputs arriving at different cortical layers. *Nature* **398**, 338–341 (1999).
  40. Larkum, M. E., Kaiser, K. M. & Sakmann, B. Calcium electrogenesis in distal apical dendrites of layer 5 pyramidal cells at a critical frequency of back-propagating action potentials. *Proc. Natl Acad. Sci. USA* **96**, 14600–14604 (1999).
  41. Bekkers, J. M. Distribution and activation of voltage-gated potassium channels in cell-attached and outside-out patches from large layer 5 cortical pyramidal neurons of the rat. *J. Physiol. (Lond.)* **525**, 611–620 (2000).
  42. Golding, N. L. & Spruston, N. Dendritic sodium spikes are variable triggers of axonal action potentials in hippocampal CA1 pyramidal neurons. *Neuron* **21**, 1189–1200 (1998).
  43. Larkman, A. U., Jack, J. J. & Stratford, K. J. Quantal analysis of excitatory synapses in rat hippocampal CA1 *in vitro* during low-frequency depression. *J. Physiol. (Lond.)* **505**, 457–471 (1997).
  44. Lim, R., Alvarez, F. J. & Walmsley, B. Quantal size is correlated with receptor cluster area at glycinergic synapses in the rat brainstem. *J. Physiol. (Lond.)* **516**, 505–512 (1999).
  45. Sorra, K. E. & Harris, K. M. Occurrence and three-dimensional structure of multiple synapses between individual radiatum axons and their target pyramidal cells in hippocampal area CA1. *J. Neurosci.* **13**, 3736–3748 (1993).
  46. Nusser, Z. *et al.* Cell type and pathway dependence of synaptic AMPA receptor number and variability in the hippocampus. *Neuron* **21**, 545–559 (1998).
  47. Takumi, Y., Ramirez-León, V., Laake, P., Rinwik, E. & Ottersen, O. P. Different modes of expression of AMPA and NMDA receptors in hippocampal synapse. *Nature Neurosci.* **2**, 618–624 (1999).
  48. Nusser, Z., Cull-Candy, S. & Farrant, M. Differences in synaptic GABA(A) receptor number underlie variation in GABA mini amplitude. *Neuron* **19**, 697–709, (1997).
  49. Korn, H., Bausela, F., Charpier, S. & Faber, D. S. Synaptic noise and multiquantal release at dendritic synapses. *J. Neurophysiol.* **70**, 1249–1254 (1993).
- Shows that the amplitude distal synaptic currents on goldfish Mauthner neurons are increased by the release of more than one single quantum of transmitter. The authors discuss evidence for an increased number of synaptic boutons with multiple release sites as the underlying mechanism for the normalization of the amplitude.**
50. Spruston, N., Jonas, P. & Sakmann, B. Dendritic glutamate receptor channels in rat hippocampal CA3 and CA1 pyramidal neurons. *J. Physiol. (Lond.)* **482**, 325–352 (1995).
  51. Otmakhova, N. A., Otmakhov, N. & Lisman, J. Is NMDA/AMPA ratio higher in perforant path-CA1 input? *Soc. Neurosci. Abstr.* **26**, 351 (2000).
  52. Geiger, J. R. P., Lübke, J., Roth, A., Frotscher, M. & Jonas, P. Submillisecond AMPA receptor-mediated signaling at a principal neuron-interneuron synapse. *Neuron* **18**, 1009–1023 (1997).
- Using an impressive combination of techniques, this paper shows how the kinetics of glutamate receptors can influence temporal integration of excitatory postsynaptic potentials (EPSPs). A specific receptor subunit composition produces rapid deactivation of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors and a greatly reduced temporal summation.**
53. Trussell, L. O. Synaptic mechanisms for coding timing in auditory neurons. *Annu. Rev. Physiol.* **61**, 477–496 (1999).
  54. Cook, E. P. & Johnston, D. Active dendrites reduce location-dependent variability of synaptic input trains. *J. Neurophysiol.* **78**, 2116–2128 (1997).
  55. Buzsáki, G. & Chrobak, J. J. Temporal structure in spatially organized neuronal ensembles: a role for interneuronal networks. *Curr. Opin. Neurobiol.* **5**, 504–510 (1995).
  56. O'Keefe, J. & Recce, M. L. Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* **3**, 317–330 (1993).
  57. Powers, R. K. & Binder, M. D. Summation of effective synaptic currents and firing rate modulation in cat spinal motoneurons. *J. Neurophysiol.* **83**, 483–500, (2000).
  58. Ferster, D. Linearity of synaptic interactions in the assembly of receptive fields in the cat visual cortex. *Curr. Opin. Neurobiol.* **4**, 563–568 (1994).
  59. Deangelis, G. C., Ohzawa I. & Freeman, R. D. Spatiotemporal organization of simple-cell receptive fields in the cat striate cortex. II. Linearity of temporal and spatial summation. *J. Neurophysiol.* **69**, 1118–1135 (1993).
  60. Steinmetz, M. A., Motter, B. C., Duffy, C. J. & Mountcastle, V. B. Functional properties of parietal visual neurons: radial organization of directionalities within the visual field. *J. Neurosci.* **7**, 177–191 (1987).
  61. Johnston, D., Hoffman, D., Colbert, C. & Magee, J. C. Modulation of backpropagating action potentials in dendrites of hippocampal pyramidal neurons. *Curr. Opin. Neurobiol.* **9**, 288–292 (1999).
  62. Mel, B. Synaptic integration in an excitable dendritic tree. *J. Neurophysiol.* **70**, 1086–1101 (1993).
  63. Archie, K. A. & Mel, B. W. A model for intradendritic computation of binocular disparity. *Nature Neurosci.* **3**, 54–63, 2000.