

Coding with spike shapes and graded potentials in cortical networks

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Summary

In cortical neurones, analogue dendritic potentials are thought to be encoded into patterns of digital spikes. According to this view, neuronal codes and computations are based on the temporal patterns of spikes: spike times, bursts or spike rates. Recently, we proposed an 'action potential waveform code' for cortical pyramidal neurones in which the spike shape carries information. Broader somatic action potentials are reliably produced in response to higher conductance input, allowing for four times more information transfer than spike times alone. This information is preserved during synaptic integration in a single neurone, as back-propagating action potentials of diverse shapes differentially shunt incoming postsynaptic potentials and so participate in the next round of spike generation. An open question has been whether the information in action potential waveforms can also survive axonal conduction and directly influence synaptic transmission to neighbouring neurones. Several new findings have now brought new light to this subject, showing cortical information processing that transcends the classical models. *BioEssays* 29:178–187, 2007. © 2007 Wiley Periodicals, Inc.

Introduction

The conventional view of signal processing in cortical neurones is that graded dendritic potentials are converted

into digital patterns of spikes (Fig. 1A). The carriers of information are then the temporal patterns of spikes or even a simpler abstraction like the spike rate (Fig. 1B). We refer to this as the 'pulse code'. At the other end of the spectrum of possibilities is the view in which all mechanisms affecting synaptic integration and transmission are relevant in the neural code (Fig. 1C). Here, we argue that the latest experimental evidence points to an intermediate situation in which some other features of the membrane potential trajectory (Fig. 1D), apart from the sequence of spike times, significantly influence synaptic output (Fig. 1E).

Our recent work⁽¹⁾ established that the different action potential (AP) shapes produced by the same pyramidal cortical neurone are not random but correspond to the level of the previous conductance. We named this phenomenon the 'AP waveform code' (Fig. 1C). The reliability of this code was found to be very high, allowing for four times more information transfer than spike times alone. We proposed that this code could influence postsynaptic targets, in at least two different ways. First, the differential interaction of APs of different shapes with incoming excitatory postsynaptic potentials (EPSPs)⁽²⁾ can influence synaptic integration. Second, variability of AP waveforms could persist until the synaptic terminal where differential calcium influx translates them into different EPSP sizes in the postsynaptic cell. Shu et al,⁽³⁾ using simultaneous somatic and axonal recordings, have now shown not only that the somatic AP waveforms survive the axonal conduction but also that the differences in the somatic waveforms are in fact further augmented by axonal conduction. Furthermore, consistent with the 'AP waveform code', the EPSPs that they recorded were larger when the presynaptic somatic and axonal spikes were broader.

However, there is a second type of code, which we call the 'background-modulated pulse code' that is also consistent with the experimental results. In this code, the subthreshold voltage on which the APs sit is the relevant biophysical signal that is influencing synaptic transmission (Fig. 1D). Recent evidence in the hippocampus⁽⁴⁾ favours this form of code. According to our calculations,⁽¹⁾ this code too can achieve very high rates of transmission. We review these results and discuss future experimental approaches for elucidating the relative importance of the different codes in neural information processing. (See Box 1.)

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Abbreviations: AP, action potential; EPSP, excitatory postsynaptic potential; LTP, long-term potentiation; PSP, postsynaptic potential.

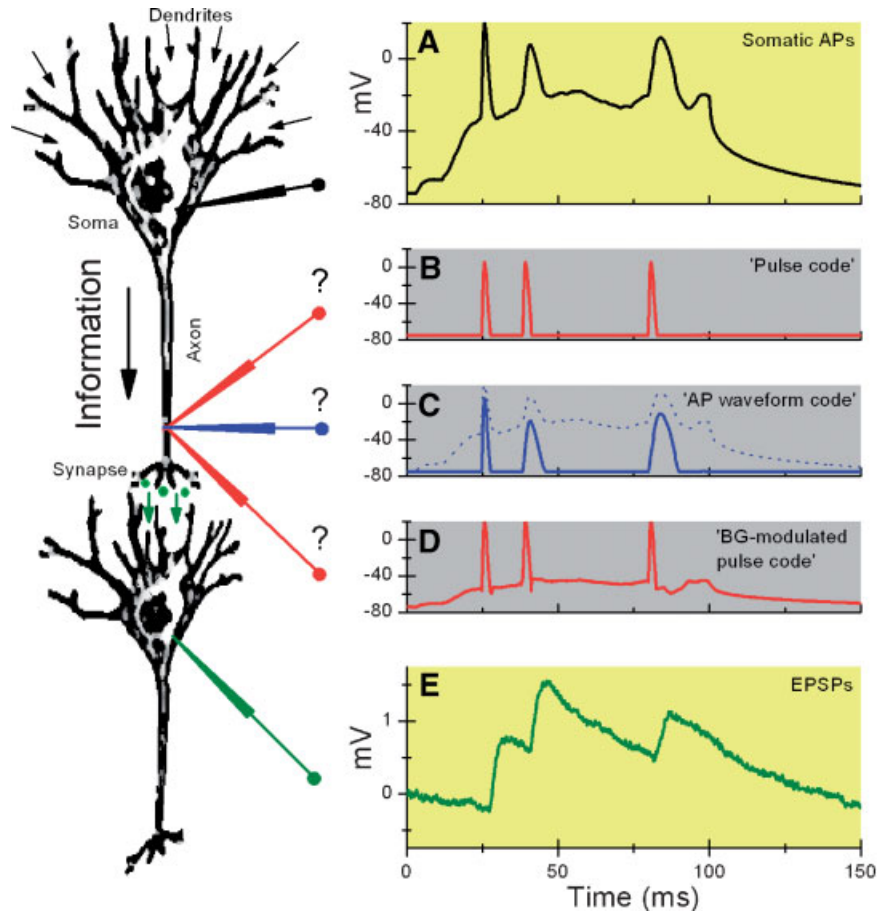


Figure 1. Schematic and highly simplified presentation of the flow and processing of information in cortical neurons. **A:** Intracellular recordings from the somata of cortical neurones have revealed that integration of naturalistic synaptic inputs (EPSPs) evokes action potential waveforms of different shapes that sit on graded voltage changes.^(1,5,13,14) **B–D:** There are three major viewpoints how this information could be used in axonal signalling. **B:** In the classical ‘pulse code’, the graded background voltage is filtered off and only stereotypical patterns of action potentials carry information. **C:** In the ‘action potential waveform code’, either the total graded waveform (dotted line) or action potential waveforms (continuous line) survives the conduction. **D:** In the ‘background-modulated pulse code’, the information about the voltage background survives the axonal conduction, modulating the gain of the synapse, whereas the spikes—irrespective of their different shapes—act only as trigger pulses for the synaptic transmission.^(3,4,29) **E:** The post-synaptic neurone encodes this information into graded EPSPs.

Encoding of input conductances into somatic AP waveforms

There are two steps required to prove that a nervous system uses a particular code. First, different inputs need to be encoded into different states of the code with a sufficiently low noise level. Second, these states need to have an impact on other neurones. We demonstrated the first of these requirements for an AP waveform code in cortical pyramidal neurones⁽¹⁾ (Fig. 2). We used specific techniques to address this question quantitatively. The conductance injection method, also called ‘dynamic clamp’,^(5–7) was used to stimulate the neurone. Although the waveform code is present in the spike responses to fixed current stimuli, as regularly seen in the traditional current-clamp experiments, the variety in AP

waveforms can only be clearly seen at the somatic level when the more natural conductance injection stimulation is used. Furthermore, the neuronal voltage responses were analyzed for information content as fully analogue signals, as previously done for the graded voltage responses of photoreceptors.⁽⁸⁾

In conductance injection, the *conductance* representing the response to patterns of presynaptic firing is applied to the cell, so that current is injected according to the instantaneous value of this conductance and the neurone’s membrane potential (Fig. 2A). This accurately reproduces the current-limiting and shunting behaviour, and the other dynamical aspects of real synaptic inputs that result from the interaction of the input with the response (membrane potential). In contrast, if the

Box 1. Terminology

Neural code is the way neurones represent changes in their external environment or in their internal state and communicate these to other neurones. It is likely that the neural code is a consequence of different structural and functional constraints^(58,59) in the nervous system, which leads communication between neurones to occur through membrane potential responses of certain properties and shapes. The neural code must be robust, having both adapting and plastic characteristics in order to cope with large environmental stimulus changes and to overcome the limitations of unreliable, slow hardware.

Information content is a measure of the number of different stimulus patterns coded as different by the neuronal response.

Rate of information transfer is the information content a neural response carries in one second. According to Shannon's information theory, any message contains two components, signal and noise.⁽⁶⁰⁾ The neural signal is the pattern of activity that a neurone wishes to communicate to its neighbours—i.e. the essence of its message, whereas the neural noise is any activity that corrupts the delivery of this message. Both the neural signal and noise can be estimated by recording neural responses to a repeated stimulus pattern. If certain statistical conditions are met,⁽⁶⁰⁾ the signal can be approximated as the average response and the noise in the responses as the difference from that average. From the ratio between the signal and the noise, one may then estimate how much rate of information transfer the neural message conveys,⁽⁶⁰⁾ in bits per second. This method has been applied to graded responses of primary sensory neurones, such as photoreceptors.⁽⁸⁾ However, it is more often the case in the nervous system that the statistical conditions for calculating the information capacity are not met.⁽⁸⁾ Particularly, analysing responses that contain action potentials require different statistical tools to work out the rate of information transfer of a neurone. Again, following the ideas of Shannon,^(1,8,60) we can calculate two important statistical measures: the richness of the neural responses (or language), called the entropy rate, and the level of errors the neural responses show at any moment of time, called the noise entropy rate. The difference between the entropy rate and the noise entropy rate gives the rate of information transfer.

experiments are done in current clamp, one inevitably injects artificial levels of current when the neurone is firing, destroying the natural encoding of AP shapes. Using conductance injection with naturalistic bursty conductance patterns,⁽⁵⁾ the

shapes of the resulting APs follow a characteristic width–height distribution (Fig. 2B).⁽¹⁾ For each spike, one can then look up its immediate conductance history (Fig. 2A). The conductance histories leading to different AP waveforms are different: higher background conductance results in broader spikes (Fig. 2C). Repetition experiments, in which the same conductance pattern is repeatedly injected into the neurone, were used to show how little noise the waveform code has (Fig. 2D). This was further quantified using information theory (Fig. 2E). For a spike rate of 10 AP/sec, a code based on AP waveforms can transmit 200 bits/sec, compared to the 50 bits/sec of one based on spike times. Moreover, the total voltage output of the neurone can carry high rates of information, similar to those shown for invertebrate photoreceptors⁽⁸⁾ and graded potential synapses⁽⁹⁾ during naturalistic stimulation (Fig. 2D).

Ways the variable AP waveforms can have an impact on other neurones

There are two possible scenarios for the waveform code to influence postsynaptic targets, indirect and direct. On the one hand, indirect influence means that different AP waveforms have an effect on subsequent AP generation. The interaction of different AP shapes with synaptic input can modify the integration of synaptic input, and thus the encoding of firing patterns. For example, Häusser and co-workers established that backpropagating APs serve as an intraneural negative feedback that regulates the integration of dendritic PSPs.⁽²⁾ The important point here is that the interaction between incoming PSPs (Fig. 3A) and a backpropagating AP (Fig. 3B,C) and, therefore, the probability of producing the next spike (Fig. 3D), depends on the AP waveform⁽²⁾ (Fig. 3E). They obtained this result experimentally by recording from two types of neurones, each with characteristically different AP waveforms, and by modelling. As each neurone was able to reproduce its own distinctive AP waveform in response to a brief repeated current pulse, one could study how the incoming PSPs were affected by interactions with backpropagated APs of a specific shape. A mechanism like theirs, but for the different AP waveforms produced by the same neurone during dendritic conductance inputs (Fig. 3D), allows for the waveform code to influence the probability of spike production and therefore the probability of PSP production postsynaptically.⁽¹⁾

On the other hand, a direct influence means that the variability in AP waveforms survives their travel along the axon to the presynaptic terminals. This would then enable the well-known calcium-dependent presynaptic mechanisms to produce, for example, higher EPSPs for broader APs.⁽¹⁰⁾ The role of a direct influence would be weakened if APs are normalized by active regeneration, or filtered by the passive properties of the axon so that the differences in the AP waveform are lost during the journey to the synapse.

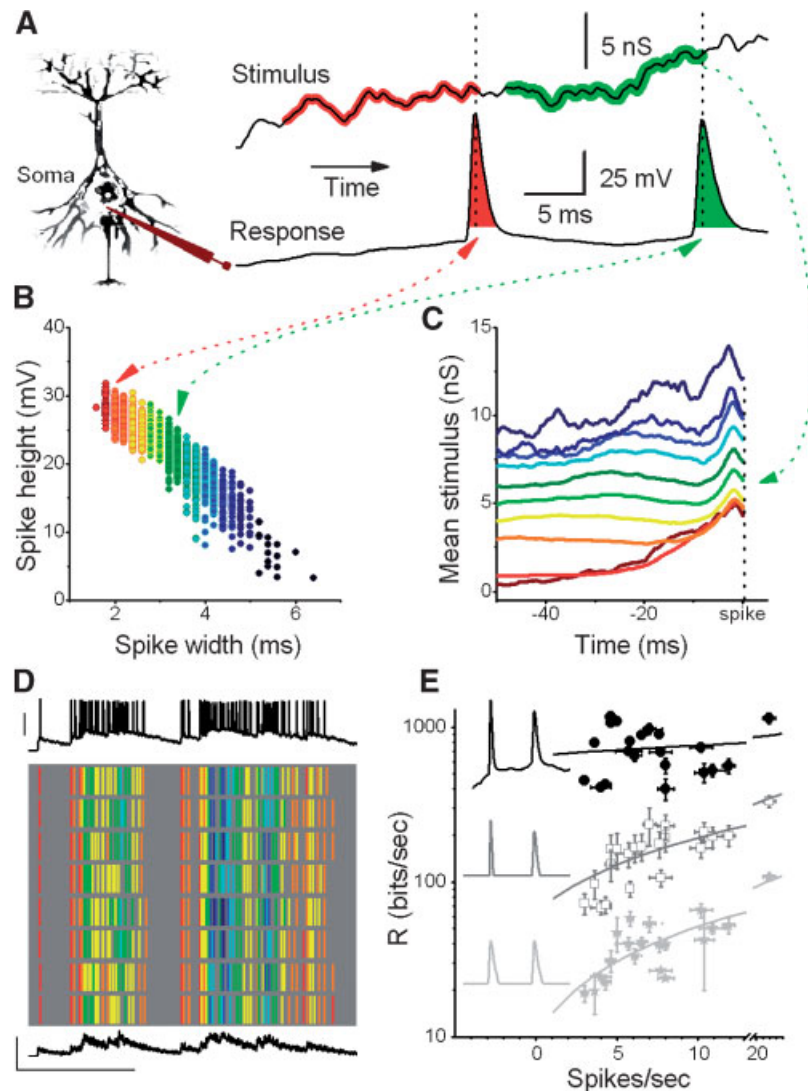


Figure 2. Somatic encoding of naturalistic synaptic inputs into action potential waveforms in pyramidal neurons of rat cortex. **A:** Rapid changes in synaptic conductances at low input levels evoke tall and slim spikes (red); at high input level, the resulting spikes are short and fat (green). **B:** Sorting the spikes by their waveforms reveals a characteristic width–height distribution. **C:** The stimulus histories leading to similar action potentials are closely related, suggesting that each action potential waveform encodes in a compressed format tens of milliseconds of stimulus history prior to firing. **D:** Experiments, in which the same naturalistic conductance pattern is repeated, show that the same action potential waveforms are reliably produced by the same stimulus history, demonstrating that there is very little noise in the encoding. **E:** Comparison of the rate of information transfer, R , for the total somatic voltage responses (black symbols), the action potential waveforms alone (grey open symbols) and the data where all the action potentials are replaced by the mean—stereotypical—action potential waveform. The action potential waveforms alone carry four times more information than pulsatile spikes. **B–E** modified from Ref. 1.

Propagation of APs in the axon

The general reliance on extracellular recordings, where it is impossible to detect changes in the action potential waveforms as they propagate along the axon, has traditionally downplayed the importance of subthreshold activity in axonal signalling in favour of digital transmission of information. In the view of the ‘pulse code’, axonal conduction works towards

normalising APs into a stereotypical form and to filter out background activity to bring about pulsatile, all-or-nothing transmitter release from the axonal terminals. These long-standing views have now been challenged by intracellular recordings from the axons of cortical neurons.

Shu et al.⁽³⁾ established a technique to record simultaneously from the soma and axon of individual cortical

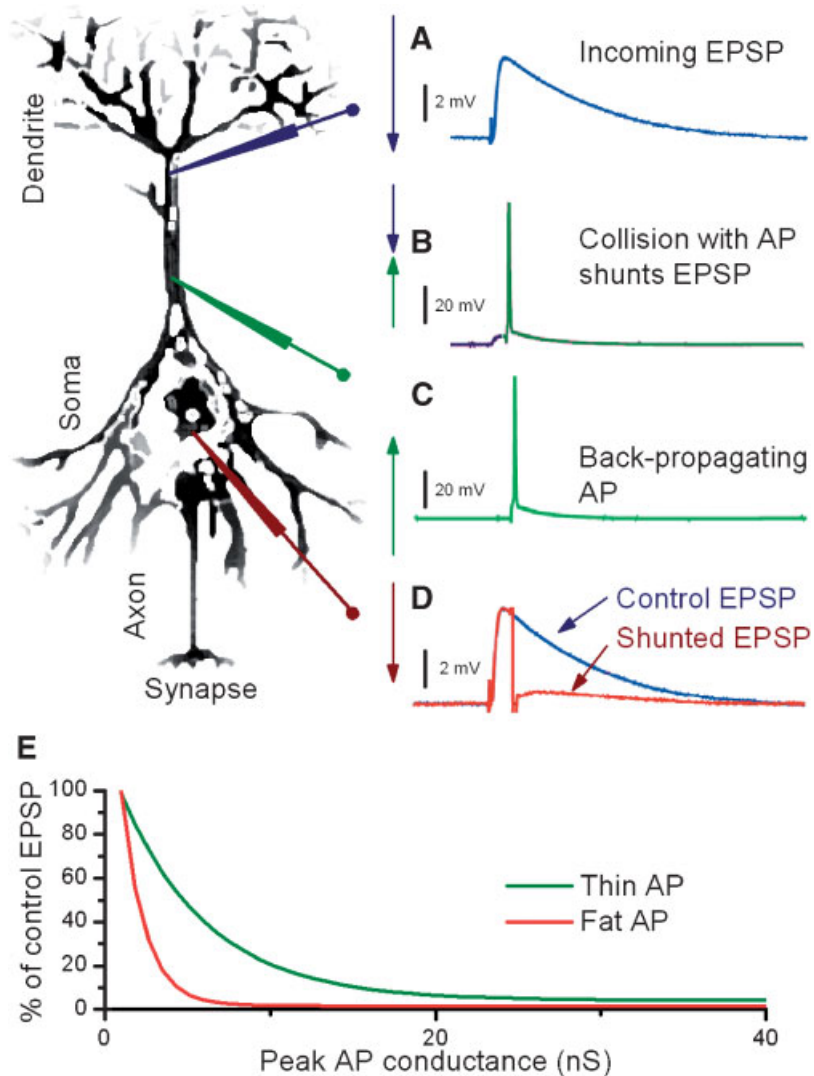


Figure 3. Differential shunting of EPSPs by back-propagating action potentials. **A:** An incoming EPSP travels from the dendrite towards the soma. **B:** When the EPSP (blue beginning of the joined trace) collides **C:** with a backpropagating action potential (green end of the joined trace), **D:** the membrane impedance is momentarily reduced at their meeting point, causing a reduction in the size of the EPSP that enters the soma. **E:** As the degree of the shunting in the EPSPs depends on the shapes of the action potentials they encounter in the dendrite, the information carried by different AP waveforms is not lost. Even in the most wasteful scenario of information being reduced into a pulse code,⁽³⁸⁾ the information in the action potential waveforms—as translated into the form of appropriately shaped EPSPs—would still participate in the timing and generation of the next round of action potentials. **A–E** modified from Ref. 2.

neurons. Using this method, they studied the axonal propagation of APs in response to brief somatic current pulses at different somatic voltage levels. Their key finding was that the d.c. length constant of axons is longer than expected, typically over 400 microns. Since this is long enough for the cortical synapses to feel somatic voltage-changes and more than the length of many axons in local networks, Shu et al.⁽³⁾ established that the mean membrane potential in the soma of a cortical neurone can extend its influence to the signalling at the synaptic boutons, at the end of its axon (Fig. 4).

When inspecting their recordings, it becomes clear that the somatic AP waveforms display the previously identified trend of wider APs being produced for higher initial voltage (or conductance) levels^(1,10) (Fig. 4A). The range of variability of APs appears similar to other current-clamp studies^(11,12) but it is smaller than in conductance injection experiments,^(1,5,13) optically controlled stimulation experiments⁽¹⁴⁾ or *in vivo* recordings.^(15–21) Importantly, even if the current-clamp stimulus led to less than natural variability in the somatic AP waveforms, their differences were greatly augmented at the axonal terminals

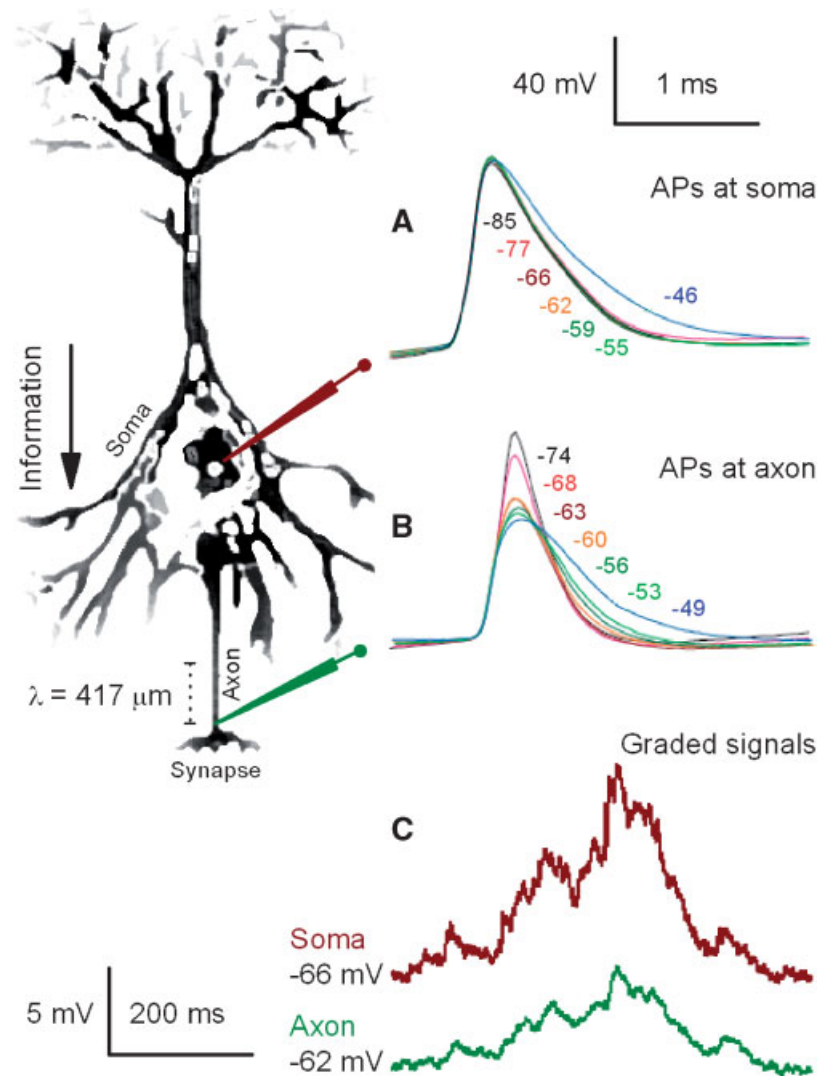


Figure 4. Axonal propagation of APs and graded signals recorded simultaneously from the soma and axon of the same cortical neurone in vitro at 34°C. **A:** By injecting brief current pulses at different backgrounds through somatic electrode, Shu et al.⁽³⁾ studied the effect the mean membrane potential has on axonal propagation of nearly identical axon potentials. The coloured numbers indicate the mean membrane potentials before each AP. **B:** Axonal propagation dramatically enhances the differences in the waveforms of somatic APs, with the fat spikes becoming shorter and fatter, and the thin spikes arriving thinner at the end on the axon terminal. Again the coloured numbers refer to the mean membrane potentials preceding each AP. The length constant, λ , of cortical axons is surprisingly long, enabling a considerable somatic influence on the signalling at the axon terminal. In addition, the variable effects on APs waveforms suggest that the axonal signal transfer is not purely passive but is influenced by local voltage—or calcium-dependent conductances. **C:** Even small subthreshold signals survive axonal conduction, with the higher signal frequencies being smoothed out⁽³⁾ the most by axonal filtering. **A–C** modified from Ref. 3.

(Fig. 4B). Furthermore, the high length constant of axons allows a significant transfer of subthreshold signals (Fig. 4C). In other words, Shu et al.⁽³⁾ showed that the axons of cortical neurones do not normalise action potentials, but instead AP waveforms in the axon seem to be able encode information via their modulation by the subthreshold potential. The information in the AP waveforms, therefore, survives axonal propagation in the cortical neurones even for relatively long distances.

Synaptic transmission of APs

Since not only APs⁽²²⁾ but also their waveforms⁽³⁾ endure the axonal conduction to the fine terminals in the brain, could then the AP waveform code also cross the synapses? Until recently this was considered highly unlikely, with cortical synapses subject both to release failures and quantal fluctuations.^(23,24) However, a great deal of the earlier work was done using brain slices at room temperature. At physiological temperatures and

settings, cortical synapses seem to function more rapidly and reliably. Furthermore, individual cortical pyramidal cells project to thousands of output synaptic contacts, so that even with highly stochastic individual synapses, the waveform code would be transmittable in the average behaviour of the synaptic population.

We now know that, at near body temperature, the presynaptic machinery of cortical neurones is fast enough to follow rapid changes in AP waveforms.⁽²⁵⁾ The calcium-channel kinetics at synaptic boutons are very fast, allowing significant calcium entry during the upstroke of the presynaptic AP, and extremely fast calcium-driven vesicle fusion, which lags behind calcium influx only by 60 μ s.⁽²⁵⁾ Furthermore, other lines of investigation have shown that the rate of failures in translating APs either to excitatory or inhibitory PSPs is very low^(26,27) and that at least the synapses in the input layer of the cerebella cortex can sustain vesicular release at very high firing rates (>300 Hz; Fig. 5A).⁽²⁸⁾ Since high rates of vesicle release can be maintained at each release site by rapid reloading of release-ready vesicles from a large releasable pool of vesicles, these synapse are able to transmit broadband information.⁽²⁸⁾ It is not surprising then that even small changes in spike width can influence neurotransmitter release as measured by postsynaptic EPSCs⁽¹⁰⁾ and EPSPs⁽³⁾ (Fig. 5B).

The last point makes the case for decoding. Can the postsynaptic neurone reliably read the messages that the presynaptic neurone is conveying? By comparing the presynaptic and postsynaptic recordings in the cortex, Shu et al.,⁽³⁾ showed in accordance with previous studies in other systems^(10,29) that wider axonal APs produce higher EPSPs (Fig. 5B). Nevertheless, these results leave open the question of whether it is the AP waveform (Fig. 5B), which through a calcium-dependent mechanism, is responsible for higher EPSPs, or it is the subthreshold voltage, as proposed for Calyx of Held (Fig. 5C) and hippocampal neurones (Fig. 5D), that is the biophysical signal modifying the synaptic output. These recent results provide evidence for both the 'AP waveform code' and the 'background-modulated pulse code'.

To further establish the functional significance of these codes, it would be interesting to record from axons while generating different somatic AP waveforms by conductance injection. As the smaller differences in somatic APs are enhanced in axons by interaction with background voltage,⁽³⁾ we expect with conductance injection that axonal AP waveforms should be even more different than those observed by Shu et al, allowing for higher information transfer in AP waveforms down the axon. However, regardless which one of the two codes turns out to be the preferred one in cortical synaptic signal transfer, they are both well suited for fast decoding of messages.

Unlike conventional pulse codes, both the 'AP waveform code' and 'background-modulated pulse code' conveniently

save processing time, as a single spike can transmit a complex message, reducing the need for spike counting. With these codes, the postsynaptic target neurone can rapidly read from PSPs the type of signals and the level of activity in the input network. This can be facilitated by synchronous delivery of the same message from many neurones, if the message is important. To envision how the fast decoding occurs, consider the simultaneous transmission of either thin or fat spikes from the input neurones. Thin APs on a low-voltage background would evoke a lower postsynaptic potential than longer lasting fat APs on a higher voltage background.

Generality of neural computations and future avenues

Recent experimental evidence, thus, has made it clear that neural computations involve complex and specific manipulations of the direction, features and interactions of signals at different parts of the neurone.^(13,30–32) Similar to a range of findings in invertebrate neurones,^(33–39) APs in cortical axons and dendrites do not just propagate but are correlated in their shape with the underlying graded signals, selectively suppressing and enhancing the transmitted activity patterns,⁽³⁾ and so participate in the neural processing of information.^(1,3–5) This correspondence across the phyla leads us to suspect that many coding principles found in invertebrate neurones could also play a role in the cortex. In the following, we highlight only a few such possibilities that may come to light in future research on vertebrate central microcircuits. However, it also appears to be the case that AP waveform coding is a specific adaptation of certain cell types with particular encoding functions—fast-spiking inhibitory interneurones in the cortex, for example, show essentially no modulation of spike shape with diverse conductance inputs.⁽⁴⁰⁾

Logical gating of APs at axonal branch points

It is feasible that some axonal branch points of cortical neurones could function as activity-dependent gates,⁽⁴¹⁾ controlling and directing the flow of signals in a switch-like manner, as has been shown for leech mechanoreceptor neurones.^(33,42) In leech neurones, APs entering the axonal branch point can have different fates. Depending on the width of the APs and the mean membrane potential,⁽³³⁾ APs are transmitted down the efferent processes or propagate back (reflected) to the axon originating the AP, or neither.⁽⁴²⁾ If we assume similar operations for cortical neurones, in which the axons often ramify to form intricate trees with contacts to thousands of target neurones,^(43,44) and bear in mind the enhanced differences in the shape of the axonal APs^(3,45) and the potential signalling constraints of small branches,⁽⁴⁶⁾ the rules for gating signals appear even more complex.

The variable changes of different AP waveforms, for instance, could sort APs with different probabilities for entering small and large diameter axonal branches. Consider, for

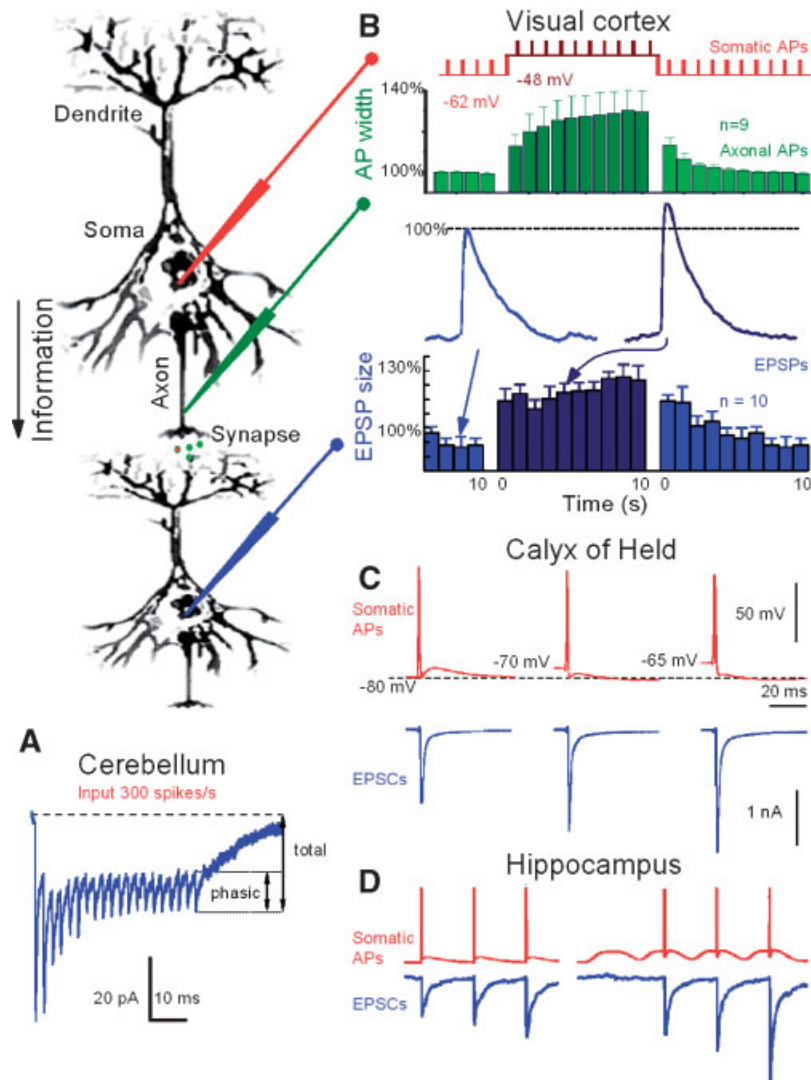


Figure 5. Signal transmission in different synapses of the brain shows both graded and pulsatile properties. The colouring in the schematic illustration of two neurones indicates the recording sites of the data (**A–D**) with red, blue and green indicating somatic, axonal and postsynaptic locations, respectively. **A:** Mean excitatory postsynaptic currents (EPSCs) during a 20-pulse train at 300 Hz measured at mossy fibre–cerebellar granule cell synapse.⁽²⁸⁾ Mossy fibres in cerebellum have small synapses yet enough vesicles for high transmission rates.⁽²⁸⁾ The phasic components are responses to individual APs, whereas the total component carries the memory of the ongoing synaptic activity. **B:** In cortex, the wider axonal APs evoke taller EPSPs.⁽³⁾ Brief depolarising current pulses of identical size, superimposed on a low (red traces) and high (purple traces) background current, are injected into the soma of a cortical pyramidal neurone in layer 5. This generates individual axonal APs of different widths; slim APs (represented by green bars) being evoked at low mean membrane potentials and fat APs (olive bars) being evoked at higher mean membrane potentials. In the postsynaptic neurones, the amplitudes of the corresponding EPSPs (blue and dark blue traces) correlate accordingly. Slim APs produce short EPSPs (the blue trace and bars) and fat APs produce tall EPSPs (the dark blue trace and bars). The time scale for the current stimulus, AP and EPSP bar graphs is the same, whereas the two representative EPSP traces last only 100 ms. **C:** In Calyx of Held APs are triggered at different mean membrane potentials (–80, –70 and –65 mV) and the corresponding postsynaptic current responses are recorded. Again the higher presynaptic voltage level correlates strongly with the larger postsynaptic responses, here EPSCs.⁽²⁹⁾ **D:** Similarly, intracellular recordings from the somata of pre- and postsynaptic hippocampal neurones have shown that the higher the presynaptic voltage level on which the APs are superimposed, the larger the EPSCs.⁽⁴⁾ **A:** modified from Ref. 28. **B:** modified from Ref. 3. **C:** modified from Ref. 29. **D:** modified from Ref. 4.

example, a cortical axon with many thick and thin branches, with each of the branches innervating separate neurones. Because of its small charge, a thin AP could only reach the synaptic boutons at the end of thinner branches—as the current that they generate in thick branches would not be sufficient for the propagation to proceed⁽⁴⁷⁾—and so to transmit information to relatively few neurones. Whereas the high charge of a fat AP could invade all the branches and signal to all the target neurones. Furthermore, depending on the geometry and the mismatching impedances of the branches at the bifurcations,⁽⁴⁸⁾ some fat APs could also reflect, thereby transiently increasing the frequency or refining the timing of APs on one side of the branch point.^(34,49) Now, consider further intra-axonal calcium dynamics. Suppose that calcium concentration or calcium-sensitive conductances⁽⁵⁰⁾ could hold a short-term memory of previous input or signal the background voltage.^(29,35) Such mechanisms could be then be used as history-dependent weighting functions to selectively route information for specific neural computations, such as motion or feature detection.

The use of AP waveforms or graded signals for LTP and axon guidance

One may also speculate that axonal AP waveforms^(3,10) or voltage levels⁽³⁵⁾ could play a role in establishing synaptic connectivity, influencing differential synaptic plasticity⁽⁴²⁾ or regrowth. If broad APs, evoked predominantly during high-activity epochs, were to increase calcium concentration of axon terminals more than thin APs of low-activity epochs, this could potentiate PSPs^(4,29,35) or guide the growth of selected branches. In cortical neural networks, such functions could, thus, be used for spatial redistribution, reorganisation or localisation of memories.

Optimising information transmission

The capacity to transmit neural information can be dynamically enhanced by using appropriately timed inhibitory and excitatory synaptic feedback and feedforward connections^(9,27) as well as voltage-gated conductances^(45,51,52) to filter presynaptic and postsynaptic responses. Moreover, similar to graded potential synapses in the fly eye,⁽⁵³⁾ presynaptic utilisation of different AP waveforms at different background voltages could further optimize the packaging of the postsynaptic responses for the transmission channel—whitening the frequency range and broadening the amplitude distribution of PSPs.⁽⁵⁴⁾

Conclusion

The use of AP waveforms or combinations of graded and pulsatile potentials in cortical neurones has now revealed computational capabilities that go beyond the expectations of the classical models. New experiments have enabled us to see how the clever usage of graded features from dendrite to soma

to axons and synapses is making neural processing more efficient than many had thought previously. Synapses still operate discontinuously, transmitting information only when the waveform of depolarisation reaches certain presynaptic voltages. But by either using the 'AP waveform code' or the 'background-modulated pulse code' this communication is significantly faster than with classical pulse codes. Furthermore, since the APs tower over the background activity and are precisely timed, they have a very high signal-to-noise ratio, carrying at least four times more information than estimated from the spikes times alone.

This new viewpoint of AP waveform coding requires a deeper theoretical understanding of spike-shape coding. For example, reduced generic bifurcation models of spike generation, with low numbers of variables, such as FitzHugh-Nagumo^(55,56) and Morris-Lecar⁽⁵⁷⁾ models, use different and biophysically unrealistic strategies for generating spike shape, and have very different capacities for spike-shape diversity. What are the essential biophysical dynamics that lead to effective spike-shape diversity? How does waveform diversity interact with noise and with subthreshold oscillations? How do phenomena such as stochastic resonance function with spike-shape diversity? What are the possibilities for neuromodulation of spike-shape coding, by expression or modification of particular ionic conductances? These questions will require modelling at a number of levels, from detailed cable models of neurons to single-compartment biophysical and reduced differential-equation models.

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