NEWS & VIEWS

NEUROSCIENCE

Spikes too kinky in the cortex?

Boris Gutkin and G. Bard Ermentrout

The Hodgkin–Huxley theory that explains the mechanism of how neurons fire forms the cornerstone of computational neuroscience. But something it hasn't predicted is happening in the brain cortex.

Neurons encode and transmit information by generating action potentials, or 'spikes' of voltage that sweep along their membranes (Box 1). It has been 50 years since Hodgkin and Huxley[1] proposed a mechanistic model by which such spikes are generated in an electrically excitable membrane. The theoretical framework associated with their model, the so-called HH formalism, is the closest that neurophysiologists have to Newton's laws of motion, and it underpins almost all modern models of how neurons work. In a bold and imaginative study, Naundorf *et al.* (page 1060 of this issue)[2] challenge the HH theory and specifically its applicability to the neurons of the cerebral cortex.

Hodgkin and Huxley[1] showed that spikes in neuronal membranes are produced through the interaction of fast depolarizing and slower hyperpolarizing currents that are dynamically dependent on the voltage (Box 1). Without knowing that voltage-dependent ion channels existed, Hodgkin and Huxley reasoned that the experimentally observed activation and inactivation curves of these currents could be explained by the collective action of a population of channels acting independently. This theory was later backed up with thermodynamical arguments[3].

A practical outcome of this framework is a family of computational models stating, in terms of differential equations, how the dynamics of the various voltage-dependent processes evolve with time. In this family of models, the currents are the product of the conductance per ion channel, the density of channels, the fraction of open channels, the membrane area and the electrical driving force due to the ion concentration gradient. One of the key tenets is that the fraction of the open channels is governed by the membrane voltage, with channels themselves being mutually independent.

The HH formalism predicts that, when viewed at high temporal precision, spikes rise smoothly once the membrane voltage reaches the activation threshold. Naundorf *et al.*[2] have tested this by recording spikes from a variety of cortical neurons *in vitro* and *in vivo*. They found that the spikes rise much more abruptly than expected from the models based on the HH formalism. Moreover, the voltage at which the spike takes off (the threshold) varies remarkably from spike to spike in the same neuron *in vivo* (Fig. 1, overleaf). Examining several HH-based models, the authors find that none of them can account for both observations — spike sharpness and threshold variability. Indeed, under the HH formalism the spike speed and onset-voltage variability seem to be antagonistic: if the model parameters are tweaked to fit the observations for spike speed, the variability in onset cannot occur and vice versa.

Naundorf *et al.* conclude that the HH formalism is not valid for the neurons that they monitored, and they propose a complementary model that invokes cooperative voltage-gated sodium channels. They took as their basis a sodium-channel model[4] that allowed for a slow voltage-independent transition from the open state to the inactivated closed state. This can produce the threshold variability: for slower inputs to the neuron the threshold is higher than for rapid inputs, as, during the slow depolarization phase, more channels are inactivated, so greater input is needed for activation.

Naundorf *et al.* then make a radical addition to this model: they allow the threshold for the voltage-dependent transition from the closed state to the open state to depend directly on the number of open channels. This channel cooperativity means that the opening of one channel makes the neighbouring channels more likely to open, providing a positive-feedback mechanism over and above the intrinsic voltage dependence of the channels. This allows sharp spike onsets without affecting the inactivation rate, leaving the onset variability intact. If channel cooperativity does occur, it should depend on the channel density, with sparser channels producing less cooperativity. So Naundorf *et al.* tested their theory by reducing the effective channel density using the sodium-channel blocker tetrodotoxin. They found that the spikes did indeed become smoother and closer to the HH model.

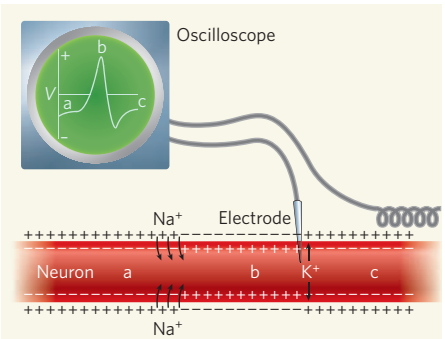
All in all, it's a tall order to contest a theory as well established as the HH model. Even if Naundorf and colleagues' theoretical proposals

Box 1 | Action potentials in neurons

The membranes of all cells have a potential difference across them, as the cell interior is negative with respect to the exterior (**a**). In neurons, certain stimuli can reduce this potential difference by opening sodium-ion channels in the membrane. For example, neurotransmitters interact specifically with ligand-gated sodium-ion channels. So sodium ions flow into the cell, reducing the voltage across the membrane.

Once the potential difference reaches a threshold voltage, the reduced voltage causes hundreds of voltage-gated sodium channels in that region of the membrane to open briefly. Sodium ions flood into the cell, completely depolarizing the membrane (**b**). This opens more voltage-gated ion channels in the adjacent membrane, and so a wave of depolarization courses along the cell — the action potential.

As the action potential nears its peak, the sodium channels close, and potassium channels open, allowing ions to flow out of the cell (the hyperpolarizing current) to restore the normal potential of the membrane (**c**).



Because action potentials are an all-or-nothing response, occurring only once the threshold voltage is reached, the strength of the stimulating signal will not produce a larger 'spike' in the neuron. Strong stimuli will instead produce a series of action potentials — so it is the frequency, number and timing of the spikes that encode neural information. **B.G. & G.B.E.**

are borne out, there are still some difficult questions to be answered. First, what are the implications for the function of cortical neurons — how does this affect the circuits they are involved in? The authors make a start at addressing this question by examining the ability of cortical neurons to respond to various input frequencies; that is, the neurons' filtering properties. They show that sharp-onset, variable-threshold neurons are likely to transmit extremely high-input frequencies while filtering out the very low frequencies — hence such neurons respond much faster than previously expected. This result may help to explain why our neurons have seemed too 'slow' to account for the speed with which we can respond to rapid stimuli (for example, in sensory discrimination experiments). On the other hand, collective behaviours in neural circuits, such as synchronization, may depend on the dynamics of spike generation (for example, see ref. 5); it remains unclear how Naundorf and colleagues' proposed mechanism would affect such large-scale dynamics.

Second, do all cortical neurons display this combination of sharp rise and variable onset? It seems that plots of voltage against the rate of change of voltage are not always as steep as those reported by Naundorf *et al.* (R. Gerkin, T. Bal and Z. Piwkowska, unpublished data). So, if there is a computational reason why some parts of the cortex have this feature, but others do not, then there are lessons to learn about how intrinsic neuronal dynamics affect the circuit properties of cortical networks.

Finally, is channel cooperativity realistic? In cell biology, cooperative behaviour and mechanisms of state-dependent self-feedback are quite common. One can even argue that voltage-dependent channels are cooperative at the population level because they depend on the membrane voltage. However, Naundorf *et al.*[2] propose a rather different level of co-operativity — direct interactions of single channels. Although such cooperativity has been proposed before[6], we know of no conclusive evidence that such interactions exist.

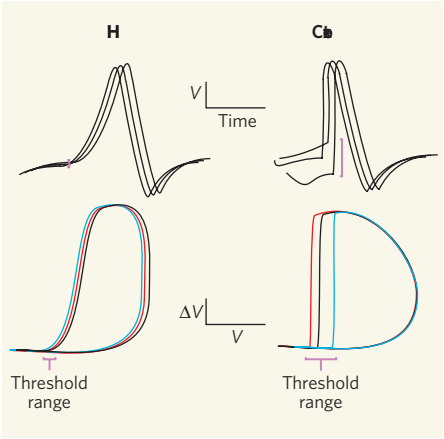


Figure 1 | Deviations from the Hodgkin–Huxley (HH) model in the cortex. The top traces show how voltage (V) changes across a specific point in the membrane, as the action potential sweeps along the neuron. The bottom graphs plot the rate of change of voltage (ΔV) against voltage, so the speed of the spike onset and the threshold voltage can be seen clearly. Under the HH formalism, spikes are smooth with a limited range of thresholds (pink brackets). However, spikes recorded in the cortex by Naundorf *et al.*[2] are sharp (vertical take-off in the bottom plot) with a wide range of thresholds *in vivo*.

But are they likely? A back-of-an-envelope calculation assuming a very high conductance, say 10,000 mS cm^{-2} (about 100 times the usual value in cortical models), and a single-channel conductance of 10 pS, suggests that individual channels would be about 10 nm apart (with a uniform distribution). Ion channels are only a few nanometres in diameter, so this may be too far apart for any direct interaction. However, there is evidence that ion channels cluster, so there might be some interactions within the clusters. Testing for the existence of such direct and local cooperative interactions will require some ingenuity from the experimental biophysics community. ■

Boris Gutkin is in the Group for Neural Theory, the Department of Cognitive Studies, ENS, and the Receptors and Cognition Department of Neuroscience, Pasteur Institute, 25 rue du Dr Roux, 75015 Paris, France.
e-mail: boris.gutkin@ens.fr
G. Bard Ermentrout is in the Department of Mathematics, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA.
e-mail: bard@math.pitt.edu

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GLACIOLOGY

Ice-sheet plumbing in Antarctica

Garry K. C. Clarke

It's not easy to work out what is going on beneath four kilometres of ice. But remote imaging has enabled the discovery of the long-distance discharge of water from one subglacial lake to another in Antarctica.

It is old news that there are lakes under the Antarctic ice sheet[1] — indeed, Earth's seventh largest lake, Lake Vostok[2], lies deep beneath the Antarctic ice. But are the lakes that form beneath great ice sheets long-lived and stable, collecting and spilling water at a steady rate? Or are they subject to cycles of filling and rapid flushing, like those that form beneath Iceland's ice caps[3]?

Spectacular landscape features, apparently sculpted by subglacial flood waters, are found in East and West Antarctica[4,5], and a flood from an unknown source was once observed on the East Antarctic ice margin[6]. But otherwise, evidence for rapid discharges has been scant — until now, that is, for Wingham *et al.*[7] (page 1033 of this issue) present convincing observations of such a flood from an Antarctic subglacial lake. The flood transferred water from a small lake near Dome C in East Antarctica to two subglacial lakes situated downslope. As a consequence, the water level in the source lake dropped by 3 metres and those of the receiver lakes rose 1 metre. This subglacial drama, inferred from changes in ice-sheet elevation monitored from a satellite some 750 kilometres above Earth's surface, occurred over a 16-month period and beneath 4 kilometres of ice.

For complicated reasons, the flow of subglacial meltwater is influenced ten times more strongly by the slope of the ice-sheet surface than by the slope of the underlying bed surface. It therefore requires a very large backslope to trap water in subglacial ponds or lakes and, as a result, ice sheets tend to expel water rather than store it[8]. Lakes tend to form near the domes of ice sheets (where the surface slope is gentle) or in deep bedrock basins (where the bed slope is steep). The lake featured in the present study is both near a dome and in a bedrock basin.

For all but the smallest lakes, the ice roof is afloat in the lake. As required by Archimedes' principle, the weight of the floating ice is supported by water pressure from the lake. This certainly holds for Lake Vostok[9], and should be true for other lakes, because ice is too weak to allow it to act as a bridge over any great distance. During discharges, the balance between the downward force exerted by ice and the upward force exerted by water is disturbed, and the unbalanced force causes the ice roof to lower as the lake level drops (Fig. 1). The descending roof can be viewed as an ice piston moving through a cylinder of ice. The motion of this piston is resisted by viscous deformation at the contact between the piston and the cylinder. If the fall in water level overtakes the