ciated with HCHWA in an Icelandic kindred[15] are primarily associated with cerebral hemorrhages. Lastly, it will be very important to know whether APPDutch mice develop cognitive impairment and, if so, whether cognition worsens with the frequency of hemorrhagic episodes.

Undoubtedly, however, this new APPDutch transgenic animal will be an invaluable model in dissecting the relative contributions of CAA and parenchymal Aβ deposition to the mechanism(s) of dementia and assessing the role of CAA in neurodegenerative processes.

1. van Duinen, S.G. *et al. Proc. Natl. Acad. Sci. USA* **84**, 5991–5994 (1987).
2. Wattendorff, A.R., Bots, G.T., Went, L.N. & Endtz, L.J. *J. Neurol. Sci.* **55**, 121–135 (1982).
3. Herzig, M.C. *et al. Nat. Neurosci.* **7**, 954–960 (2004).
4. Van Broeckhoven, C. *et al. Science* **248**, 1120–1122 (1990).
5. Levy, E. *et al. Science* **248**, 1124–1126 (1990).
6. Prelli, F. *et al. Biochem. Biophys. Res. Comm.* **170**, 301–307 (1990).
7. Castaño, E.M. *et al. J. Biol. Chem.* **271**, 32185–32191 (1996).
8. Tomidokoro, Y. *et al. Neurobiol. Aging* **25**, 38 (2004).
9. Wisniewski, T., Ghiso, J. & Frangione, B. *Biochem. Biophys. Res. Comm.* **179**, 1247–1254 (1991).
10. Miravalle, L. *et al. J. Biol. Chem.* **275**, 27110–27116 (2000).
11. Melchor, J.P. & van Nostrand, W.E. *J. Biol. Chem.* **275**, 9782–9791 (2000).
12. Monro, O.R. *et al. Neurobiol. Aging* **23**, 405–412 (2002).
13. Götz, J. *et al. Mol. Psychiatry* 1–20 (2004).
14. Davis, J. *et al. J. Biol. Chem.* **279**, 20296–20306 (2004).
15. Revesz, T. *et al. J. Neuropathol. Exp. Neurol.* **62**, 885–898 (2003).

Conducting synaptic music in dendrites

Michael London & Idan Segev

Thousands of active synapses on the dendrites drastically increase membrane conductance. Williams now shows that local processing is unaffected by conductance changes in distant regions, highlighting how functionally independent dendritic regions interact.

Imagine yourself on the floor of the stock market on a busy day, trying to get the attention of your broker on the other side of the room. You shout as loudly as you can, but it's no use—your voice is lost in the din of the crowd right around him. This is the problem faced by a synapse on the dendritic tree of a pyramidal neuron. It might have an important message to deliver to the axon, but thousands of other synapses are also contacting the dendritic tree. When active, each synapse opens a tiny hole in the membrane, allowing ions to flow through the membrane so that, all together, the conductance of the membrane becomes very high and the message of our synapse may be lost (shunted) before it reaches the axon. Welcome to the high-conductance state[1].

In this issue, Williams[2] asks whether increases in membrane conductance resulting from intense synaptic activity at the somatic region could interfere with the integration of synaptic inputs at the distal apical tuft, and vice versa. To date, this issue had only been addressed through simulations in compartmental models of neurons[1]. Using the 'dynamic clamp' method[3,4] and skillful multiple recordings from proximal and distal dendritic sites *in vitro*, Williams showed that the synaptic conductance change at one site was essentially invisible at the other. As a consequence, synaptic integration continued uninterrupted at these sites. Williams also found that synaptic messages from the distal sites affected the output of the proximal soma–axon region. This distal-to-proximal communication was implemented via dendritic spikes that started distally and propagated forward to the soma. Therefore, despite the large shunt that synaptic activity imposed on the dendritic tree, synaptic integration could take place almost independently at several dendritic regions, whereas dendritic spikes enabled the output of these regions to be reliably heard at the axon (**Fig. 1**).

For many years, it was unclear how synapses succeed in being such good matchmakers, forming interactive and communicative networks from isolated neurons. Is this matchmaking enabled via chemical or via electrical interaction between neurons? This "soup versus spark" controversy[5] has ended with the triumph of the soup (of neurotransmitters).

One consequence of chemical communication between neurons is that neurotransmitter release transiently changes the conductance of the postsynaptic membrane (a transient membrane shunt). Because of these transient changes in membrane conductance of the postsynaptic neurons, the temporal summation of individual postsynaptic voltage responses is sublinear. That is, when two synapses are activated together, the voltage response is less than the linear sum of the responses of each synapse individually, as first demonstrated for central neurons by Burke[6]. However, when recording at the soma, it is often hard to detect conductance changes accompanying synaptic transmission of distal dendritic synapses[7]. Theoretical studies[8,9] have suggested that this is a consequence of the partial electrical isolation imposed by the cable properties of dendrites on remote synapses. Until the present study, though, the degree and functional consequences of this electrical isolation were never examined directly.

In technically challenging experiments, Williams made four simultaneous recordings from a layer-5 pyramidal neuron *in vitro*: two proximal and two very distal in the apical tree. To simulate the effects of many thousands of synapses impinging either proximally or distally, Williams used the dynamic clamp technique, which was invented about 10 years ago[3,4]. By creating a hybrid between the computer (which controls the amount of current injected via an intracellular electrode) and the recorded neuron, synaptic conductance changes (in series with a battery) were modeled as a current source, which depends on the (freely changing) postsynaptic membrane potential (a 'voltage-dependent current source'). This is in contrast to the voltage-clamp technique, in which the current injected via the intracellular electrode enforces a predetermined value for the postsynaptic membrane potential.

Williams first asked to what extent the shunt introduced by synaptic conductance at one location affects synaptic integration at the other. To address this question, he introduced a step conductance change in either the dendrites or the soma, and measured the resulting change in input resistance along the apical dendrite. He found that compared to the voltage attenuation along the dendrite, the 'region of influence' of the conductance change was much smaller. In other words, the 'visibility' of conductance change as a function of distance

Michael London is at the Wolfson Institute for Biomedical Research, University College London, London WC1E 6BT, UK. Idan Segev is at the Interdisciplinary Center for Neural Computation and Department of Neurobiology, Hebrew University, Jerusalem, 91904, Israel.
e-mail: m.london@ucl.ac.uk

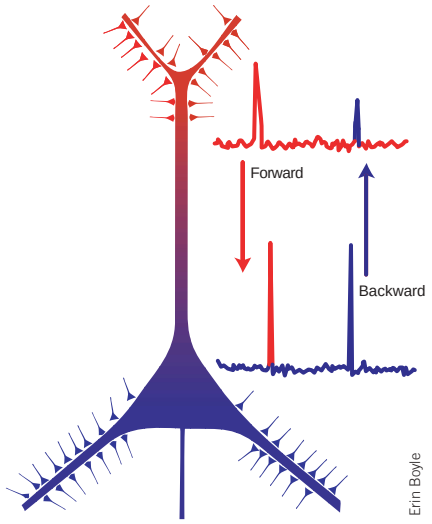

Figure 1 The compartmental pyramidal neuron. The picture emerging from recent studies, and highlighted by Williams, is of pyramidal cells having essentially two compartments that are independent in terms of subthreshold synaptic integration: one basal-somatic region (blue) and one apical region (red). These two compartments communicate through suprathreshold spikes, which can overcome the local synaptic shunt and propagate both in the forward and backward direction along the apical dendrite.

was much more limited than the visibility of voltage change, which is in agreement with previous theoretical predictions[8,9]. Thus, even if many synapses are active in the soma and basal tree, the integration of synapses in the apical dendrites is essentially unperturbed (and vice versa). One could also imagine that, to a lesser degree, synaptic bombardment on one branch on the apical tuft will only moderately affect synaptic integration on neighboring branches. The degree of 'conductance invisibility' is what defines how many functional compartments a neuron would have[10,11]. In principle, the more independent compartments for synaptic integration that a neuron might have, the less it resembles a 'point neuron', in which all synapses are integrated at one point (the soma). This might increase the capability of the neuron to distinguish between the activity of different groups of inputs and, thus, increase the overall computational power of the neuron[11,12].

Williams showed that the somatic and the distal dendritic tuft compartments of layer-5 pyramidal neurons could integrate synaptic input independently. But there is a sting in the tail: if the distal compartment does not interact with the proximal one, then what good is synaptic integration at distal sites? Williams also demonstrated that communication between these two sites is achieved via suprathreshold active spikes that propagate along the apical dendrite.

The apical dendrite contains voltage-gated ion channels that can support back-propagation of Na^+ action potentials (BPAPs) from soma to dendrites[13]. There is also a second initiation zone for Ca^{2+} spikes at, or near, the apical tuft[14]. This latter finding supports the notion that the apical dendrite might have its own independent integration point for distal synaptic inputs to affect, via a powerful local Ca^{2+} spike, the output at the soma. However, it has been unclear whether these dendritic spikes are functional *in vivo*, as the high-conductance state may destroy the initiation and propagation of dendritic spikes, thereby blocking communication between the different functional compartments. In the current study, Williams demonstrated that in spite of large synaptic conductance load at the soma, distal spikes propagated safely toward the soma to trigger additional axonal output spikes. Williams also demonstrated that BPAPs could still propagate from the axon to the dendrite. Theoretical work[15] has suggested that spike amplitude is very sensitive to the conductance load imposed on the dendrites and that under most conditions, back-propagation is more secure than forward propagation. It was therefore surprising to find in Williams' work that spike amplitudes tended to decrease more in the reverse direction than in the forward direction.

To summarize, Williams shows that the view of a pyramidal neuron as consisting of two major compartments (**Fig. 1**) holds even under the tough conditions imposed by the high membrane conductance state that is assumed to be the typical *in vivo* situation. This high-conductance state, on the one hand, sharpens the distinction between the two compartments in the subthreshold regime, yet it still enables communication between the two compartments via suprathreshold signals.

However, the dynamic clamp method has a major limitation, namely that the simulated conductance change can be introduced at only the location where the intracellular electrode contacts the neuron. *In vivo* during the high-conductance state, synapses are distributed all over the dendritic surface and the dendritic membrane is shunted throughout. This may have significant consequences for forward as well as backward propagation of dendritic spikes.

Another point to consider functionally is the role of the forward-propagating action potentials in dendrites. In addition to propagating toward the soma, it is likely that these spikes propagate to side branches at the apical tree (thus becoming 'back-propagating' spikes there). These same spikes also propagate forward to fire axonal spikes, which also might back-propagate to the dendrites. So how do all these forward and backward dendritic spikes interact and make sense of the messages that they are trying to convey? New optical imaging and stimulation techniques might give complementary answers to the questions posed above.

Moreover, when composing the conductance used through the dynamic clamp, Williams made some assumptions about the nature of background synaptic activity *in vivo*. It will be crucial to determine the validity of these assumptions about the high-conductance states experimentally.

Lastly, it will be important to resolve whether the local effect of synaptic shunt supports even finer compartmentalization (for example, on individual dendritic branches). Could synapses on these branches integrate their messages locally and then use local dendritic spikes to transmit the result to the axon[12]? Alternatively, perhaps dendrites do operate in a global manner, in which dendritic spikes are initiated only for spatially distributed (rather than localized) dendritic input?

Recent experiments hint that the apical tuft of pyramidal neurons is a special kind of beast. It acts as a neuron within a neuron, integrating its own inputs and having its own spike-initiation zone. Other members of this species might be the distal dendrites of Purkinje and mitral cells. Our challenge for the coming years will be to look even more closely into these special nonlinear dendrites to understand how the abundance of voltage-dependent and synaptic channels in dendrites enables neuronal networks to respond so richly to the world.

1. Destexhe, A., Rudolph, M. & Pare, D. *Nat. Rev. Neurosci.* **4**, 739–751 (2003).
2. Williams, S.R. *Nat. Neurosci.* **7**, 961–967 (2004).
3. Sharp, A.A., O'Neil, M.B., Abbott, L.F. & Marder, E. *J. Neurophysiol.* **69**, 992–995 (1993).
4. Robinson, H.P. & Kawai, N. *J. Neurosci. Methods* **49**, 157–165 (1993).
5. Cowan, W.M. & Kandel, E.R. in *Synapses* (eds. Cowan, W.M., Sudhof, T.C. & Stevens, C.F.) 1–87 (Johns Hopkins Univ. Press, Baltimore, 2001).
6. Burke, R. E. *J. Neurophysiol.* **30**, 1114–1137 (1967).
7. Smith, T. G., Wuerker, R. B. & Frank, K. *J. Neurophysiol.* **30**, 1072–1096 (1967).
8. Rall, W. *J. Neurophysiol.* **30**, 1138–1168 (1967).
9. Koch, C., Douglas, R. & Wehmeier, U. *J. Neurosci.* **10**, 1728–1744 (1990).
10. Koch, C., Poggio, T. & Torre, V. *Phil. Trans. R. Soc. Lond. B Biol. Sci.* **298**, 227–263 (1982).
11. Hausser, M. & Mel, B. *Curr. Opin. Neurobiol.* **13**, 372–383 (2003).
12. Polsky, A., Mel, B. W. & Schiller, J. *Nat. Neurosci.* **7**, 621–627 (2004).
13. Stuart, G. J. & Sakmann, B. *Nature* **367**, 69–72 (1994).
14. Larkum, M. E., Zhu, J. J. & Sakmann, B. *Nature* **398**, 338–341 (1999).
15. Rapp, M., Yarom, Y. & Segev, I. *Proc. Natl. Acad. Sci. USA* **93**, 11985–11990 (1996).