the AIS (Fig. 2f) than in the soma (Fig. 2c), as we found for real neurons (Fig. 1c, f).

We found that several other Hodgkin–Huxley models of cortical pyramidal cells, even one based on a relatively low density of Na^+ conductance in the axon, replicated the 'kink' and variability of somatic spikes (Fig. 2 legend). These features of spike initiation in the soma were dependent on the initiation of spikes in the AIS: increasing the somatic Na^+ conductance to a high level (7.5 nS μm^{-2}) and removing Na^+ conductance from the axon in the model presented here resulted in a loss of the kink at the foot of the spike (soma slope, 4.1 ms^{-1}) and a reduction in spike threshold variability in the soma (results not shown).

Our findings reveal that leading Hodgkin–Huxley models of cortical pyramidal cell spike initiation capture the so-called unique features observed by Naundorf *et al.*[1]. We attribute these features simply to recording from a site that is distant from the site of spike initiation and to the non-uniform distribution of spike properties over the somatic and axonal membrane. The initiation of spikes in the axon that then back-propagate into the soma can result in a rapid change in membrane potential (the kink) at the foot of the somatic spike. The large current supplied by the axonal spike precedes and overlaps with the current supplied by the local generation of the action potential in the soma during the rising phase of the spike. This results in a more rapid rise at the foot of the spike in the soma than would occur if there were no preceding spike in the axon. The apparent high threshold variability with intrasomatic recordings merely results from membrane potential differences between the soma and the actual site of spike initiation, the axon, at the time that spikes are generated. These membrane-potential differences arise from local electrophysiological differences, as well as spatial non-uniformity in synaptic activity. We conclude that the observations made by Naundorf *et al.*[1] are predictable by Hodgkin–Huxley theory and the known physiology of spike initiation[2–4], and that there is no need to invoke exotic interchannel cooperativity to explain their observations.

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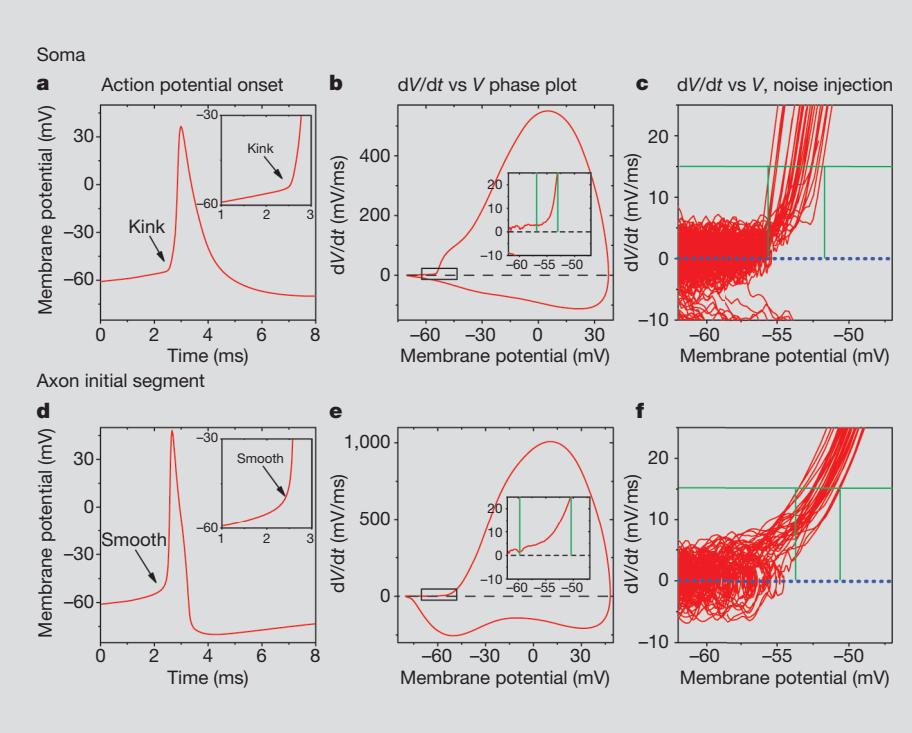

Figure 2 | Hodgkin–Huxley model of a layer-5 cortical pyramidal cell. a, Somatic spike shows a 'kink' at its onset, as in the real neuron. **b,** Phase plot (dV/dt versus V) and close-up of rapid initiation (inset) of the spike shown in **a**. **c,** Close-up of the phase plot of somatic spike during noisy intrasomatic current injection, showing a broad distribution of thresholds (green lines). **d,** Axonal spike (45 μm from the soma). **e,** Phase plot of the axonal spike. Note the smoothly rising dV/dt. **f,** Overlay of dV/dt versus V for the onset of axonal spikes, showing lower variability of spike threshold (green lines).
Methods. Results were obtained from a model layer-5 cortical pyramidal cell[13] with the intrasomatic injection of a 10–15 mV noisy conductance. The model contained the following conductances: soma (Na^+, 0.75 nS μm^{-2}; K^+, 0.15 nS μm^{-2}); axon hillock and initial segment (Na^+, 7.5 nS μm^{-2}; K^+, 1.5 nS μm^{-2}); dendrite (Na^+, 0.1 nS μm^{-2}; K^+, 0.002 nS μm^{-2}; M-current, 0.0003 nS μm^{-2}). Axonal length, 50 μm; soma size, 20 × 30 μm. These parameters were used to match the maximal dV/dt rates, durations and initiation site of spikes in our neurons (Fig. 1). Similar results are obtained from several Hodgkin–Huxley models of cortical pyramidal cells, including those using a high, medium or relatively low density of axonal Na^+ conductance[12–14], and the results from these simulations were well within the range of real cortical cells (see also www.mccormicklab.org).

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1. Naundorf, B., Wolf, F. & Volgushev, M. *Nature* **440,** 1060–1063 (2006).
2. Palmer, L. M. & Stuart, G. J. *J. Neurosci.* **26,** 1854–1863 (2006).
3. Stuart, G., Schiller, J. & Sakmann, B. *J. Physiol.* **505,** 617–632 (1997).
4. Shu, Y., Duque, A., Yu, Y., Haider, B. & McCormick, D. A. *J. Neurophysiol.* doi:10.1152/jn.00922.2006 (2006).
5. Pare, D., Shink, E., Gaudreau, H., Destexhe, A. & Lang, E. J. *J. Neurophysiol.* **79,** 1450–1460 (1998).
6. Shu, Y., Hasenstaub, A., Duque, A., Yu, Y. & McCormick, D. A. *Nature* **441,** 761–765 (2006).
7. Colbert, C. M. & Johnston, D. *J. Neurosci.* **16,** 6676–6686 (1996).
8. Coombs, J. S., Curtis, D. R. & Eccles, J. C. *J. Physiol.* **139,** 232–249 (1957).
9. Shu, Y., Hasenstaub, A., Badoual, M., Bal, T. & McCormick, D. A. *J. Neurosci.* **23,** 10388–10401 (2003).
10. Inda, M. C., DeFelipe, J. & Munoz, A. *Proc. Natl Acad. Sci. USA* **103,** 2920–2925 (2006).
11. Komada, M. & Soriano, P. *J. Cell Biol.* **156,** 337–348 (2002).
12. Colbert, C. M. & Pan, E. *Nature Neurosci.* **5,** 533–538 (2002).
13. Mainen, Z. F. & Sejnowski, T. J. *Nature* **382,** 363–366 (1996).
14. Baranauskas, G. & Martina, M. *J. Neurosci.* **26,** 671–684 (2006).

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Naundorf et al. *reply*

Replying to: D. A. McCormick, Y. Shu & Y. Yu *Nature* 445, 10.1038/nature05523 (2007)

McCormick *et al.*[1] question whether the rapid onset and highly variable thresholds of action potentials[2] are genuine features of cortical action-potential generators — that is, whether they reflect the voltage-dependence of the underlying sodium currents. Instead, they consider these features to be epiphenomena, reflecting lateral currents from a remote initiation site, and, contrary to direct evidence[3], they assume that sodium currents show canonical kinetics.

Although the lateral current hypothesis of

McCormick *et al.* is superficially plausible, their recordings are inadequate for showing that the dynamics of axonal action-potential initiation conforms to the canonical model. Their so-called axonal recordings are actually obtained from 'blebs' — injury-induced swellings of cut axons on the slice surface. The injured axons, when forming blebs, reorganize their entire cytoskeleton, including the destruction of the sub-membrane spectrin network[4] that integrates sodium channels into the supramolecular machinery of the normal initial segment[5]. As the behaviour of axonal sodium channels is highly sensitive to their cellular environment[6], the smooth action-potential waveforms in the blebs, instead of revealing the true dynamics of action-potential initiation, are more likely to be caused by the disorganized state of the bleb membrane.

The model of McCormick *et al.*[1] does not conform with the known physiology of layer-5 pyramidal cells. Contradicting direct measurements[7,8], it assumes a high ratio of axonal-to-somatic sodium currents. Even with these physiologically unrealistic settings, their model still does not reproduce the experimental data. In their *in vitro* recordings, as in our *in vivo* recordings (Fig. 2 (panels a, c) in ref. 2), somatic action potentials rise almost vertically out of the cloud of subthreshold fluctuations. In their model, however, the range of action-potential onset potentials hardly overlaps with the range of subthreshold fluctuations, being shifted towards more depolarized potentials (Fig. 2 (panel c) in ref. 1). The model of McCormick *et al.* therefore in fact provides further evidence that canonical models are incapable of correctly describing the observed dynamics of action-potential initiation[2,3].

However, McCormick *et al.* highlight an important issue. How can the action-potential dynamics at a remote initiation site be critically probed, when action-potential waveforms recorded from thin processes, such as axons, are likely to be compromised by technical problems[9]? Our analysis identifies an essentially non-invasive approach for addressing this question (see supplementary information of ref. 2). It is based on quantifying the ability of a neuron to phase-lock its spikes to a weak test stimulus in the irregular firing regime[2,10,11].

Theoretical studies indicate that canonical generators of action potentials have a very limited ability to encode high-frequency inputs, showing cut-off frequencies of phase-locking (v_c) that are of the order of their mean firing rate[10,11]. By contrast, models with intrinsically high onset rapidness (r) can show arbitrarily high cut-off frequencies[2,10–12]. If the rapidness of the action-potential onset is genuinely increased by a factor of 10, then cut-off frequencies above 100 Hz are predicted by dimensional analysis ($v_c \propto r$), even for mean firing rates of around 10 Hz. Both *in vivo* and *in vitro* studies have revealed signatures of such fast responses in the neocortex[12,13], supporting genuinely rapid initiation of action potentials in cortical neurons (see also http://www.nld.ds.mpg.de/actionpotentials).

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1. McCormick, D. A., Shu, Y. & Yu, Y. *Nature* **445,** doi:nature05523 (2007).
2. Naundorf, B., Wolf, F. & Volgushev, M. *Nature* **440,** 1060–1063 (2006).
3. Baranauskas, G. & Martina, M. *J. Neurosci.* **26,** 671–684 (2006).
4. Spira, M. E., Oren, R., Dormann, A., Ilouz, N. & Lev, S. *Cell Mol. Neurobiol.* **21,** 591–604 (2002).
5. Lacas-Gervais, S. *et al. J. Cell Biol.* **166,** 983–990 (2004).
6. Rush, A. M., Dib-Hajj, S. D. & Waxman, S. G. *J. Physiol.* **564,** 803–815 (2005).
7. Colbert, C. M. & Pan, E. *Nature Neurosci.* **5,** 533–538 (2002).
8. Ruben, P. C., Ilscher, S. U., Williams, S. R. & Stuart, G. *J. Soc. Neurosci.* abstr. 476.2 (2003).
9. Waters, J., Schaefer, A. & Sakmann, B. *Progr. Biophys. Mol. Biol.* **87,** 145–170 (2005).
10. Fourcaud-Trocme, N., Hansel, D., van Vreeswijk, C. & Brunel, N. *J. Neurosci.* **23,** 11628–11640 (2003).
11. Naundorf, B., Geisel, T. & Wolf, F. *J. Comput. Neurosci.* **18,** 297–309 (2005).
12. Silberberg, G., Bethge, M., Markram, H., Pawelzik, K. & Tsodyks, M. *J. Neurophysiol.* **91,** 704–709 (2004).
13. Williams, P. E., Mechler, F., Gordon, J., Shapley, R. & Hawken, M. J. *J. Neurosci.* **24,** 8278–8288 (2004).

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