TO THE EDITOR—The recent study by Magee and Cook¹ in CA1 pyramidal neurons in vitro (see also ref. 2) raises a fundamental issue. Is the dependence of somatic EPSPs on the location of the dendritic synapses, which is expected from dendritic filtering, a ‘bug’ that should be rectified (for example, by mechanisms that eliminate voltage attenuation in the dendritic tree), or is this dependence a ‘feature’ that enhances the computational capability of the neuron? Magee and Cook’s direct synaptic conductance change enhances the computational capability of the dendritic tree, away from the soma. This progressive increase in synaptic conductance gives rise to location-independence of soma EPSPs on the location of the dendritic arborization¹ and, functionally, the neuron could be treated as a ‘point neuron’.

But is it valid to assume that if, in vitro, the size of individual somatic EPSPs is independent of the dendritic input location, this would also remain true when many synapses bombard the dendritic tree, as is the case in vivo? We show that in the latter case, the location-independence found in the quiescent in vitro condition is lost, and distal synapses become weaker at the soma than do proximal synapses (Fig. 1a; see web supplement, http://www.nature.com/neuro/web_specials/, for detailed figure legend). This is the result of a several-fold increase in dendritic membrane conductance, Gm, due to the activity of many synapses in vivo³–⁶. In other words, precisely the same mechanism of synaptic conductance change that is used for scaling up distal synapses destroys the ‘location independence’ (it is ‘self defeating’) when the network is active.

The general argument is that if, in some reference cases, the scaling of synaptic conductance gives rise to location-independent EPSP amplitude at the soma, any change in Gm will instantaneously eliminate this property. In particular, if Gm increases, the somatic EPSPs from distal sites will decrease relatively more than do somatic EPSPs that originate proximally. This can be demonstrated using the simplest case of an infinitely long passive uniform cylinder with linear steady-state current inputs (Iin). Voltage attenuation with distance in this case is exponential, V(x) = V(x=0) e⁻¹⁄²(Gm), where λ = d/(4RiGm) is the space constant, d is the cylinder diameter and R is the specific axial resistance. In order to generate the same V at some point (for example, at x = 0) for all input locations, Iin(x) must increase as e⁻¹⁄² to compensate for the exponential attenuation of V.

If Gm is increased uniformly by some factor, then λ is reduced by the square root of this factor, and a steeper profile of Iin(x) is now required for preserving location-independence V at x = 0. The scaling that was sufficient to preserve location-independence prior to the increase in Gm is now insufficient, particularly for large x values (such as distal synapses). For example, if the distal and proximal input sites are 1A apart and the distal input is scaled such that V(x=0) is identical from the two sites, then increasing Gm by a factor of 4 results in a distal input that is only 37% of the proximal input at x = 0.

The effect of network activity that is likely to be found in vivo on the degree of location-independence of somatic EPSP amplitude is simulated using a model of a CA1 neuron (Fig. 1a). In the ‘in vitro’ case, a progressive increase in Gm with distance (Fig. 1b) removes the location dependence and produces unitary somatic EPSPs with a 0.2 mV peak for all input locations (example in Fig. 1a, ‘in vitro’ case). This location independence is abolished due to network activity (Fig. 1c). First we show that a uniform increase in Gm over the dendrites, resulting in a 4-fold reduction in soma input resistance, Rm (similar to the experimental findings)⁴–⁶, significantly weakens (by a factor of 5 at x = 600 μm) distal synapses (that are ‘location-independent’ in vitro) as compared to proximal synapses (black line in Fig. 1c). The other two cases in Fig. 1c incorporate the synaptic scaling (shown in Fig. 1b) that preserves the in vitro location-independence into the in vivo simulations.

Note that in these three cases, the reduction in Rm underestimates the actual reduction found in vitro (25% reduction for blue and red cases, 50% for the green case). Because distal synapses induce larger local conductance changes compared to proximal synapses, the distal dendritic membrane becomes more shunted (and more depolarized, an effect that was not simulated here) when many similar excitatory synapses bombard the dendritic tree. This ‘self-defeating’ mechanism (Fig. 1c) dramatically weakens distal synapses, and this effect is robust under a wide range of model parameters.

It is possible to circumvent the mutual synaptic shunt and still use the synap-
Synchrony with other groups of synapses is face, as assumed in Fig. 1. Rather, groups asynchronously over the dendritic surface. As a condition? One possibility is that synaptic scaling independent EPSPs' in the mechanism to generate 'local dependence found in CA1 neurons. Figure 2b, green line). For larger groups (blue and red lines), the average composite somatic EPSP from distal locations was attenuated relatively more than it was in the reference asynchronous case (black line). This is due to significant voltage saturation when a large number of up-scaled synapses are co-activated distally. Moreover, composite EPSPs from distal synapses are further attenuated because they are likely to encounter substantial shunt resulting from the synchronous activity of other more proximal groups of synapses.

Using a steeper synaptic scaling (Fig. 2c, red line), it is still possible to obtain location-independent somatic EPSP for a given in vivo condition (Fig. 2c, horizontal red dots). However, as soon as the network statistics change (for example, the average background firing rate increases) the location independence is instantaneously lost (Fig. 2c, green dots). In addition, achieving location independence for a given in vivo condition is critically dependent on the target somatic EPSP value and on the dendritic morphology, and in many cases (for example, for red dots beyond 550 µm) this is impossible to obtain with reasonable values for the synaptic conductance change.

Other membrane mechanisms, such as voltage-dependent amplification could still render distal and proximal synapses equally effective at the soma, even in the presence of network activity. Still other voltage-dependent mechanisms such as \( I_k \) and \( I_h \) currents, as well as synaptic inhibition, are expected to effectively increase \( G_m \), thus intensifying the location dependence of somatic EPSP amplitude. It remains to be shown experimentally whether, indeed, dendritic attenuation is actually removed in the in vivo condition. Such experiments are currently feasible, including intracellular recordings from pairs of synaptically connected neurons in vivo, as well as the use of two-photon microscope for measuring unitary somatic EPSPs following the activation of a single dendritic synapse.

The main purpose of this letter is to emphasize that the behavior of unitary synaptic EPSPs found in vivo is bound to be markedly different when the neuron is embedded in an active network. Experiments confirm that network activity changes the cable properties of the postsynaptic neuron dramatically. The mechanism of synaptic scaling that preserves 'location independence in vivo is highly sensitive to dendritic cable properties, and it is, therefore, highly unlikely that this mechanism will retain location independence of somatic EPSP amplitude in the dynamic transitions (and fluctuations) that neuronal networks undergo in vivo (for example, in CA1). Whether the location dependence of somatic EPSPs is a 'bug' or a 'feature' will be resolved if we continue to listen to what neurons (as well as synapses) tell us, while keeping in mind that in many instances, what they say in vivo is not necessarily what they say in vitro.

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Note: The source code for the simulations in this work and detailed figure legends are available at http://www.nature.com/neuro/web_specials/

REPLY—We welcome the intent of the letter by London and Segev to reaffirm the well-known fact that network activity can change the cable properties of neurons (also see ref. 13 for further references). We show the same effect in Figure 4d (ref. 1), and one of us has recently published papers specifically on this issue. We do not agree, however, with the supposition that computer simulations using unrealistic model neurons can tell us much of substance about synaptic integration under in vivo conditions. If computer models are to provide enhanced understanding of neuronal integration, they need to reflect as closely as possible the conditions they wish to simulate.

London and Segev's passive dendrite model contains too many assumptions and omissions to justify their conclusions. The most glaring omission is a lack of voltage-dependent conductances in the dendrites; active properties can completely alter synaptic integration and the overall electrical behavior of dendrites. For example, in a model containing Na⁺ and Ca²⁺ channels, increased synaptic activity might generate locally initiated spikes rather than the saturation to 0 mV shown by London and Segev. Models that incorporate K⁺ channels show that these channels can regulate the amplitudes of EPSPs, the threshold for local spikes, and the shapes, amplitudes and frequency of back-propagating spikes. Also, H⁻ channels will reduce the location dependence...
of EPSP decay and temporal summation, and thereby drastically alter the way in which dendrites respond to the patterns of inputs used by London and Segev.

Other problems in the model by London and Segev include the use of uniform synapse types and synaptic densities (for example, proximally located inhibition produces much of the somatic shunting seen in vivo)\(^{14}\), the use of very slow kinetics for AMPA conductances (more realistic kinetics would increase the required synchrony that was used by London and Segev)\(^{15}\), and the complete omission of voltage-dependent NMDA conductances (NMDARs reduce the impact of the type of network activity used by London and Segev)\(^{16}\). We would also like to remind readers that our data and conclusions covered input from only a single synaptic pathway, which is located in the region of the dendrites that is the least sensitive to London and Segev’s simulated changes in input patterns. (Schaffer collaterals are within \(\sim 300 \mu m\) of the soma.) Whether other more distal pathways might use the same normalizing mechanism or be normalized to the same level is simply unknown (although the large size, complicated geometry and sparse density of tuft spines suggest that they may indeed have a larger conductance)\(^{16}\).

In short, we find the modeling of London and Segev to be accurate and informative only within the confines of examining the impact of synaptic conductances on passive cables. Given what we now know about dendritic physiology, we believe that their simulations do not present a realistic picture of neurons in vivo.

It is clear that neuronal dendrites are far more than passives cables and, as a result, support a wider range of functionality than depicted by the model of London and Segev. Furthermore, CA1 pyramidal neurons should indeed discriminate among different spatio-temporal patterns of synaptic input, but not in the way suggested by the passive cable model of London and Segev.\(^{17}\) We would expect CA1 dendrites to be capable of linearly summating lower levels of synaptic activity without respect to location (at least for Schaffer collaterals)\(^{18}\). However, we do not believe that the most important result of increased synaptic activity is a change in the cable properties of the dendrites. Instead, we predict that high levels of synaptic input will move dendrites into a completely different integration mode, one that is more nonlinear and that perhaps includes local spike initiation\(^{8}\) (see ref. 17 for further references). Such a wide range of processing is made available by the wonderfully complex, nonlinear properties of dendrites.

In closing, it is true that dendritic cable properties are a foundation upon which dendritic function is constructed. However, when one views a remarkable structure, it is always most enlightening to look at more than just its foundation.

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