Synaptic scaling *in vitro* and *in vivo*

TO THE EDITOR—The recent study by Magee and Cook[1] 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 dendritic measurements show that the synaptic conductance change, g_{syn}, becomes larger as one moves along the apical dendrite, away from the soma. This progressive increase in g_{syn} counterbalances the voltage attenuation imposed by dendritic cable properties, and consequently, the amplitude of unitary somatic EPSPs is insensitive to its dendritic origin ('location-independent' somatic EPSPs). If the location dependence of soma EPSPs is indeed removed, then "…all synapses will have the same ability to initiate action potentials and to induce long-term synaptic plasticity regardless of their location in the dendritic arborization"[1] 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. 1**; 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, G_m, due to the activity of many synapses *in vivo*[3–6]. 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 G_m will instantaneously eliminate this property. In particular, if G_m 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 (I_{in}). Voltage attenuation with distance in this case is exponential, $V(x) \propto e^{-x/\lambda}$, where $\lambda = \sqrt{(d/(4R_iG_m))}$ is the space constant, d is the cylinder diameter and R_i is the specific axial resistance. In order to generate the same V at some point (for example, at $x = 0$) for all input locations, $I_{in}(x)$ must increase as $e^{x/\lambda}$ to compensate for the exponential attenuation of V. If G_m is increased uniformly by some factor, then λ is reduced by the square root of this factor, and a steeper profile of $I_{in}(x)$ is now required for preserving location-independent V at $x = 0$. The scaling that was sufficient to preserve location-independence prior to the increase in G_m is now insufficient, particularly for large x values (such as distal synapses). For example, if the distal and proximal input sites are 1λ apart and the distal input is scaled such that $V(x=0)$ is identical from the two sites, then increasing G_m 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 g_{syn} 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 G_m over the dendrites, resulting in a 4-fold reduction in soma input resistance, R_{in} (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 three curves 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 R_{in} underestimates the actual reduction found *in vivo* (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.

Is it possible to circumvent the mutual synaptic shunt and still use the synap-

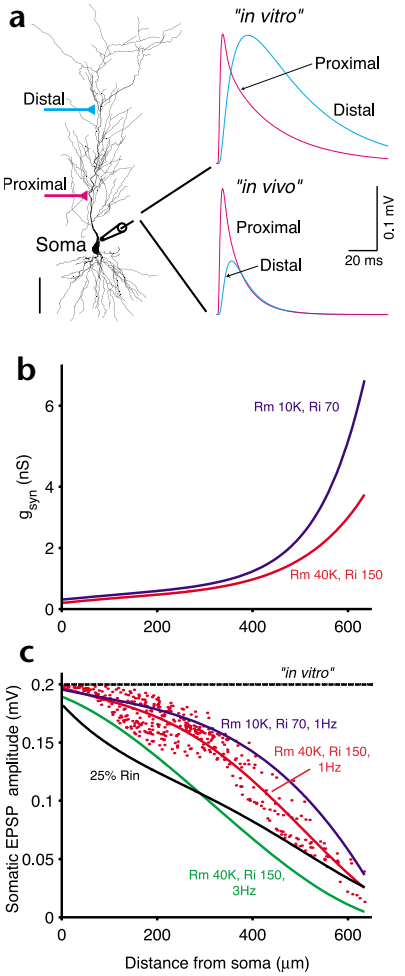

Fig. 1. Network activity eliminates the location independence of somatic EPSP amplitude found *in vitro*. See web supplement, http://www.nature.com/neuro/web_specials/, for detailed figure legend.

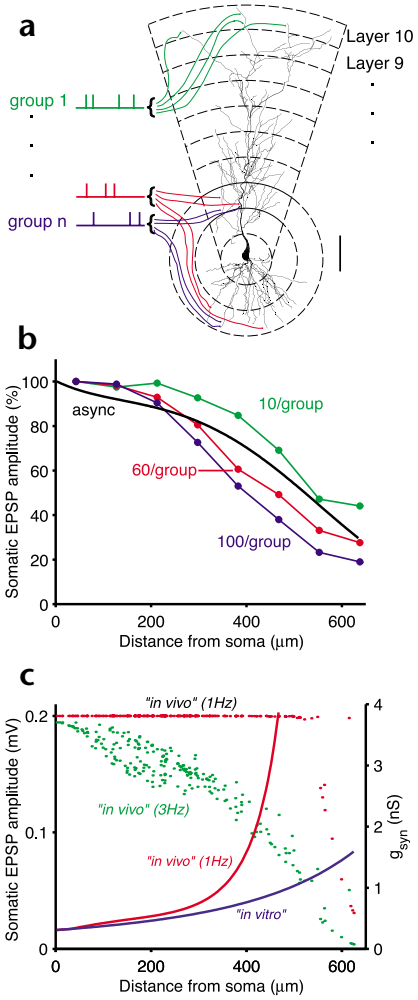

Fig. 2. Attempting to restore location-independence of somatic EPSP amplitude *in vivo* using the mechanism of synaptic scaling. See web supplement, http://www.nature.com/neuro/web_specials/ for detailed figure legend.

tic scaling mechanism to generate 'location independent EPSPs' in the *in vivo* condition? One possibility is that synapses *in vivo* are not activated randomly and asynchronously over the dendritic surface, as assumed in Fig. 1. Rather, groups of equally distant synapses may fire in synchrony among themselves and out of synchrony with other groups of synapses (**Fig. 2a**). Such temporally coherent and spatially stratified synaptic activation could potentially reduce the mutual shunting effect described above, and might partially restore the location independence of the somatic EPSP amplitude found in CA1 neurons *in vitro*. Figure 2b illustrates the results for different group sizes (10, 60 and 100 synapses per group). Surprisingly, the location independence found *in vitro* was partially restored only for the small group size (**Fig. 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[7] 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_h and I_A 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 vitro* 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 vitro* 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[6]). Whether the location dependence of somatic EPSPs is a 'bug'[8] or a 'feature'[9] 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 vitro* is not necessarily what they say *in vivo*.

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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[11] (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[12, 13]. 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[8]; active properties can completely alter synaptic integration and the overall electrical behavior of dendrites. For example, in a model containing Na^+ and Ca^{2+} 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)[13]. 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 ~300 μm 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[9] (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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