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Axonal properties determine somatic firing in a model of *in vitro* CA1 hippocampal sharp wave/ripples and persistent gamma oscillations

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Abstract

Evidence has been presented that CA1 pyramidal cells, during spontaneous *in vitro* sharp wave/ripple (SPW-R) complexes, generate somatic action potentials that originate in axons. ‘Participating’ (somatically firing) pyramidal cells fire (almost always) at most once during a particular SPW-R whereas non-participating cells virtually never fire during an SPW-R. Somatic spikelets were small or absent, while ripple-frequency EPSCs and IPSCs occurred during the SPW-R in pyramidal neurons. These experimental findings could be replicated with a network model in which electrical coupling was present between small pyramidal cell axonal branches. Here, we explore this model in more depth. Factors that influence somatic participation include: (i) the diameter of axonal branches that contain coupling sites to other axons, because firing in larger branches injects more current into the main axon, increasing antidromic firing probability; (ii) axonal K⁺ currents; and (iii) somatic hyperpolarization and shunting. We predict that portions of axons fire at high frequency during SPW-R, while somata fire much less. In the model, somatic firing can occur by occasional generation of full action potentials in proximal axonal branches, which are excited by high-frequency spikelets. When the network contains phasic synaptic inhibition, at the axonal gap junction site, gamma oscillations result, again with more frequent axonal firing than somatic firing. Combining the models, so as to generate gamma followed by sharp waves, leads to strong overlap between the population of cells firing during gamma the population of cells firing during a subsequent sharp wave, as observed *in vivo*.

Keywords

gap junction; axonal branch; transient K⁺ current; antidromic spike

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Introduction

In the awake rat, theta/gamma hippocampal oscillations occur during locomotion, with place-cell firing of pyramidal neurons; there is overlap between the neurons firing during theta/gamma and those firing during sharp wave/ripples (Buzsáki, 1986; Buzsáki et al., 1992; Lee & Wilson, 2002; Suzuki & Smith, 1985; Wilson & McNaughton, 1994; Ylinen et al., 1995), associated with immobility. The overlap could have cognitive relevance (Carr et al., 2011).

Cellular mechanisms of brain phenomena can sometimes be investigated with *in vitro* slices and network simulations, motivating *in vivo* experiments. Progress has been made with ‘persistent’ hippocampal gamma oscillations (Fisahn et al., 1998; Traub et al., 2000) and sharp wave/ripples (SPW-R; Maier et al., 2003; review in Traub & Whittington, 2010), revealing unexpected similarities in mechanism; the similarities are relevant because they could help explain why the same neurons tend to fire in both states.

- i. Both persistent gamma and SPW-R can occur in isolated CA1 as well as CA3 (Traub et al., 2003; Maier et al., 2003, 2011).
- ii. Both are associated with network oscillations at $>\sim 100$ Hz [‘very fast oscillations’ (VFO; Traub et al., 2003; Maier et al., 2003)]. VFO also occurs during theta/gamma *in vivo* (Sullivan et al., 2011) and in SPW-R *in vivo* (Buzsáki et al., 1992).
- iii. Pyramidal cell somatic firing rates are low (Fisahn et al., 1998; Bähner et al., 2011).
- iv. Perisomatic synaptic inhibition occurs (Fisahn et al., 1998; Traub et al., 2003; Bähner et al., 2011).
- v. GABA_A receptors have excitatory effects in s. oriens, where pyramidal cell axon collaterals occur (Traub et al., 2003; Bähner et al., 2011).
- vi. Pyramidal cell axons are active (Fisahn et al., 2004; Pietersen et al., 2009; Traub et al., 2003). Modeling predicts antidromic spikes (Traub et al., 2000), confirmed for SPW-R *in vitro* (Papatheodoropoulos, 2008; Bähner et al., 2011). Spikelets occur in hippocampal pyramidal cells of awake, exploring rats, in a state when gamma oscillations are expected (Epsztein et al., 2010).
- vii. Very high frequency synaptic currents and potentials occur in pyramidal cells and interneurons (Bähner et al., 2011; Maier et al., 2011; Traub et al., 2003).

The *in vitro* data suggest a role for pyramidal cell axons in gamma oscillations and in SPW-R. The data also indicate that in a slice manifesting SPW-R, a defined subset of pyramidal cells fire somatic action potential(s) during SPW-Rs whereas the remaining pyramidal cells do not (Bähner et al., 2011); this is consistent with ‘cell assemblies’ (Reichinnek et al., 2010) and reminiscent of the *in vivo* situation, in which particular cells fire during SPW-Rs.

Network models account for the *in vitro* data on gamma oscillations (Traub et al., 2000, 2003) and SPW-R (Traub & Bibbig, 2000; Bähner et al., 2011). Here, we explore features of pyramidal cell axons that allow the SPW-R model to work, and show how the gamma and SPW-R models can be unified to allow switching between respective states, suggesting how axon properties (Debanne, 2004; Bucher & Goaillard, 2011) might let the same neurons fire in both states.

Materials and methods

The overall network structure developed from that briefly described in Böhner et al. (2011), which in turn descended from, and used a programming style explained in, Traub et al. (2005). The model is schematic in nature, although it generates voltage traces that can look real. We considered it impossible to replicate precise values for conductance and connectivity parameters, and did not attempt to do so; instead, the model was designed to illustrate features of the collective neuronal activities that look like experiments, and that lead to experimental tests that might falsify various (or all) model properties.

The network contained 4,000 ‘CA1 pyramidal neurons’, 200 basket cells, 100 bistratified interneurons, 40 ‘axoaxonic’ cells and 100 oriens/lacunosum–moleculare (OLM) interneurons. Each model neuron contained multiple compartments (88 for pyramids, 59 for interneurons), divided amongst soma, branching dendrites and axon (branching in the case of pyramidal cells). Each compartment in turn contained a repertoire of ionic conductances, whose basic character is described in Traub et al. (2005), but with some modifications as below; for the present model, the most important conductances were $g_{Na(F)}$ (transient Na^+), $g_{K(DR)}$ (delayed rectifier), $g_{K(A)}$ (transient inactivating ‘A’ type K^+ conductance) and $g_{K(M)}$ (mediating so-called M-current, an intermediate timescale, non-inactivating, K^+ conductance). For the sake of simplicity, slow after hyperpolarization currents and persistent g_{Na} conductances were zero, and high- and low-threshold g_{Ca} conductances were small enough to be negligible.

Some properties of the pyramidal cells are explained further below. Basket cells, bistratified cells and axoaxonic cells were simulated as fast-spiking interneurons, using code from Traub et al. (2005). OLM cells were simulated with the ‘LTS’ (low-threshold spiking) interneuron code of the same paper. The axoaxonic interneurons simulated here may or may not correspond to chandelier cells, as our model interneurons contact axonal branches; there are neocortical parvalbumin-negative interneurons that contact axons (Gonchar et al., 2002), and axoaxonic synapses distal to the initial segment have been described in spinal cord (Llewellyn-Smith et al., 1995). However, whether fast-spiking interneurons can in fact contact axonal branches of hippocampal pyramidal neurons remains to be determined, to the best of our knowledge.

The network contained chemical synapses, with AMPA, $GABA_A$ and NMDA receptor-mediated conductances, although NMDA conductances were small enough to be negligible and will not be discussed further. In addition, there were gap junctions between interneurons (Connors & Long, 2004) and between pyramidal cell axons (Schmitz et al., 2001). The latter sort of gap junctions make an essential contribution to the present model.

Model pyramidal cells

Although the repertoire of intrinsic currents was derived from Traub et al. (2005), a neocortical model, we used the hippocampal soma–dendritic compartmental structure of Traub et al. (1994), with 64 soma–dendritic compartments. The axon, however, was modified (Fig. 1), to allow (schematically) for distant antidromic stimulation, and for two axonal branches. There are now 24 axonal compartments, including the two branches of four compartments each. In the initial segment and main trunk, compartments were 30 μm long, and radius 1.3 μm for the first 60 μm , then 0.55 μm . Axonal branch compartments were 20 μm long; for the proximal branch, radii were 0.25 μm and for the distal branch, radii ranged from 0.24 to 0.25 μm for cell nos 1,...,1000, and were 0.15 μm for the remaining cells, in effect partitioning the neurons into two discrete subsets (in order to highlight differences in behavior correlated with axonal diameter). Note that axons of diameter as small as $\sim 0.1 \mu m$ have been described (Perge et al. (2012)). For the sake of simplicity, we did not include

myelin (although Popovic et al., 2011, suggest that axonal collaterals emerge at nodes of Ranvier in layer V pyramidal neurons).

Axonal ionic conductance densities varied as well, across various compartments within a given axon, and when comparing two different axons. Thus, $g_{Na(F)}$ density ranged from 500 to 900 mS/cm² over the axon, but was 100 mS/cm² over the shaft between the two branches. [If axon collaterals indeed extend from nodes of Ranvier (Popovic et al., 2011), this region of lower $g_{Na(F)}$ density would correspond to an internode.] This Na⁺ conductance distribution allowed antidromic spikes, originating in the proximal branch, to be able to propagate to the soma, but spikes originating in the distal branch would generally fail because of attenuation at the branch point and along the inter-branch shaft. $g_{K(DR)}$ density was 700 mS/cm² over the entire axon, except for the most proximal three compartments where it was 1050 mS/cm². $g_{K(A)}$ was absent in these most proximal compartments and at the distal tip, and was 325 mS/cm² over the two branches. Along the distal shaft, it ranged from 520 to 780 mS/cm², being lower for cells 1, 2, 3... and highest for cells 3998, 3999, 4000. Along the middle shaft (between the two branches), it was 2158 mS/cm² for 'lowest' cells, ranging to 3237 mS/cm² for the 'highest' cell. Branch diameter and A-conductance density were distributed according to cell number in order to make recognition easier, as there were systematic differences in cell behavior that correlated with these parameters. These variations in axonal branch diameter and $g_{K(A)}$ made critical differences in whether pyramidal cell somata would fire during gamma oscillations and sharp waves (see Results).

Another source of variability and inhomogeneity between pyramidal cell axons consisted of small bias currents, up to 0.017 nA per compartment, which were different between compartments in one axon, and between the axons of different cells.

Axonal gap junctions were located in the distal branch (see the asterisk in Fig. 1), and had a conductance of 0.0 to 7.5 nS. Conductances in the mid and upper parts of this range would allow an action potential to cross from one axon to another (Mercer et al., 2006; Wang et al., 2010). Ectopic spikes were induced by randomly occurring brief depolarizing current pulses, to the distal tips of the distal axonal branches, at frequencies (per axon) ranging from 0 to 4 Hz.

Synaptic and gap junctional connectivity

Both types of connectivity were structured, in that inputs from cell type A to cell type B always would contact a defined subset of compartments; but were random in terms of which particular pairs of cells were connected, subject to constraints of the sort 'each cell of type B receives inputs from so many cells of type A'. Some of the details are as follows: pyramid–pyramid connections were always to basal dendrites, and any one pyramid received synaptic excitation from 10 others. Each pyramidal cell also received inputs from 40 basket cells (perisomatic), 20 OLM cells (distal apical dendrites), 40 bistratified cells (mid-basilar and apical dendrites), and 20 'axoaxonic' cells (at the gap junction site). Each interneuron received input from 40 pyramidal cells.

Pyramidal cell axons had an average of 2.25 gap junctional connections to other pyramidal cell axons, chosen randomly; the number of gap junctions on a single axon was thus Poisson-distributed (so that some axons did not connect to any others). With this density of gap junction connections, ~ 85% of the pyramidal neurons lie on the 'large cluster' (Traub et al., 1999): any pair of such neurons are connected either directly, or indirectly along a gap junctional chain. All other neurons have the property that they are not connected to any neuron of the large cluster, and hence either lie on small clusters, or else are completely isolated (electrically) from other neurons. Very fast network oscillations are thus generated entirely by those pyramidal cells on the large cluster. Interneuron gap junctions formed

between dendrites of basket cells (average 2.5 gap junctions per cell), and between dendrites of OLM cells (average 8 per cell), with conductance 1.0 nS.

Synaptic conductances had time courses of the form $\text{scaling factor} \times t \exp(-t/\tau)$, for AMPA receptors, with $\tau = 2$ ms on pyramidal cells (and scaling factor 1 nS), and 0.8 ms on interneurons (scaling factors 1 nS for basket and bistratified cells, 0.4 nS for axoaxonic cells and 0.1 nS for OLM cells). Inhibitory conductances rose abruptly and decayed exponentially, with $\tau = 30$ ms for all OLM output synapses, 2 ms for other synapses on interneurons and 8 ms for other synapses on pyramidal cells. Inhibitory scaling factors onto pyramidal cells were 1 nS (basket), 0.5 nS ('axoaxonic'), 0.4 nS (bistratified) and 0.03 nS (OLM).

Synaptic outputs of the interneurons developed when there was an overshooting action potential in the most distal axonal compartment. For pyramidal cells, the criterion was an overshooting action potential in the tip of the distal axonal branch (which was arbitrarily taken to reflect connectivity to nearby neurons, as opposed to connectivity to the subiculum or elsewhere).

Induction of various types of network behaviors

We induced SPW-R and/or a theta/gamma state with two sorts of protocols.

Protocol 1 was used for repeating SPW-R at 1.1–2.0 Hz. In this case, between SPW-Rs, pyramidal axons were electrically uncoupled and ectopic action potentials were shut off. During SPW-Rs, pyramidal cell gap junction conductance was typically 5.5 nS peak (up to 9.0 nS was tried), with time course following a half-sinewave (see Fig. 2A), and during SPW-Rs, mean ectopic rates were 1 Hz per axon. Ectopic axonal spikes were induced with 3-nA, 400- μ s current pulses to the distal six compartments of the main axonal trunk. Bias currents to interneurons were steady at 0.02–0.04 nA (basket cells), 0.0 nA ('axoaxonic' cells), 0.00–0.02 nA (bistratified cells) and –0.2 nA to OLM cells [effectively shutting them off (Klausberger et al., 2003)].

Protocol 2 was used to produce 1.5 s of 'theta/gamma' at 5 Hz, with gamma waves superimposed on the intracellularly-depolarizing part of theta (Soltesz & Deschênes, 1993); theta/gamma was then followed by SPW-R at 2 Hz. To accomplish this, we used time-dependent alterations of pyramidal cell gap junction conductance, of ectopic spike rates, and of interneuron bias, as follows:

- Pyramidal gap junction conductance was 7.5 nS during theta/gamma and during SPW-R, but 0.0 nS otherwise.
- Axonal ectopic rates were 4 Hz per axon during theta/gamma and during SPW-R, and 0.0 Hz otherwise. Ectopic spikes were induced by 2.5 nA, 0.4 ms current pulses to the distal two compartments of the distal axonal branch.
- Bias currents to 'axoaxonic' cells were 0.05 nA for 150 ms, alternating with 0.3 nA for 50 ms, during theta/gamma. The first phase approximately corresponds to the depolarizing part of theta, and allows these interneurons to fire in response to recurrent synaptic excitation but to be silent otherwise. With the 0.3-nA currents these interneurons fire spontaneously, independent of recurrent excitation. After theta/gamma, these interneurons were biased at –0.3 nA, which effectively silenced them.
- Bias currents to OLM cells were 0.6 nA during the hyperpolarizing phases of theta (50 ms duty cycle, 5 Hz), causing them to fire at high rates and help produce the

hyperpolarization. The bias current was -0.2 nA at all other times, virtually silencing the OLM cells.

- Bias currents to other interneurons were 0.02 – 0.04 nA to basket cells and 0.00 – 0.02 nA to bistratified cells.

Field measurements were made in one dimension, along an axis from stratum lacunosum–moleculare to stratum oriens, using a spatially weighted average of soma and dendritic transmembrane currents, similar to Traub et al. (2005).

Code was written in Fortran, for the mpi parallel environment, and was compiled with the mpixlf command. Execution took place on 20 nodes of an IBM 7040-681 AIX parallel machine. Simulation of 2.4 s of ‘neuronal time’ required ~ 19 hours of machine time. Source code is available through RDT at rtraub@us.ibm.com.

Results

Model can generate repeating SPW-R with sparse antidromic somatic action potentials, phase-locked to the field

Extending the model described in Böhner et al. (2011), Fig. 2 shows that the model was able to account for many of the experimentally observed features of *in vitro* SPW-Rs, provided that pyramidal cell gap junction conductances and ectopic spike rates were time-dependent. Such replicated features included the high-frequency ($> \sim 200$ Hz) component to the field, the somatic firing of only certain pyramidal neurons (Fig. 2B), the antidromic nature of somatic spikes (which arise from hyperpolarizations *in vitro*; Fig. 2B, bottom trace), the tight correlation of population somatic firing with the field (Fig. 2B, left inset) and the high-frequency components to excitatory and inhibitory synaptic currents (Fig. 2B, right inset; see also Maier et al., 2011). Note that, because somata were hyperpolarized during the SPW-R, somatic action potentials *per se* could not be attributed to phasic synaptic inputs, although the precise timing of the action potentials might be influenced by such inputs. What most needs to be explained, however, is why certain pyramidal cell somata fired at all and others did not. While a simulation model cannot be expected to provide a definitive explanation, by itself, it can suggest specific possibilities that might then be explored experimentally.

To this end, it helps to list how, in the model, pyramidal cells were different from one another. The model was constructed so that three types of parameters are variable between cells: (i) axonal anatomy, in that the diameter of the distal axonal branch could vary (see Fig. 5); (ii) the density of axonal $g_{K(A)}$ (specifically, on the main shaft), which was lowest for cell no. 1 and highest for cell no. 4,000, and distributed linearly with cell number; and (iii) axonal bias currents, which were distributed randomly and which were small. In addition, variability could arise because of network architecture: for example, the number of gap junctions on an axon, in a randomly constructed network such as we used, will be Poisson-distributed. Some axons would have no gap junctions at all, and the corresponding cells could not participate in collective behavior except as a result of ectopic activity. There was also randomness in the synaptic connectivity: not in the number of inputs per cell, but in where on the cell inputs were located. Finally, randomness arose dynamically because ectopic spikes occurred randomly, now in this axon, now in that axon; however, this type of randomness would not be expected to lead to a well-defined partition between participating and non-participating cells.

Of these factors potentially influencing participation, the easiest to analyze with a model are the systematic parametric differences between cells, and we concentrated on those factors in this paper. In order to proceed, we noted that as somatic action potentials were antidromic we should concentrate on events in respective axons: the properties of some axons may

allow distal axonal spikes to occasionally invade the soma, whereas other axons may lack said properties.

Participating cells are distinguished from non-participating cells by having larger spikelets in the proximal branch, from which full action potentials may originate

Fig. 3 contrasts the membrane events in the axonal branches, between a participating cell (left) and a non-participating cell (right), during a simulated SPW-R (the same one as illustrated in Fig. 2B). Several features are of note:

- i. In each case, the distal branch fires at high frequency, a result of ectopic spikes and electrical coupling in the distal branches (Traub et al., 1999); this high-frequency firing is absent when gap junction conductances are too small (not shown).
- ii. There is a 1:1 correspondence between action potentials in the distal branch and spikelets in the proximal branch. Inspection of voltages along the path from distal branch to proximal branch shows that there is attenuation at the branch between distal branch and main trunk (Fig. 3B), along the low-safety-factor region of the main trunk between branches, and upon entering the proximal branch (not shown).
- iii. Spikelets in the participating cell proximal branch are larger than in the non-participating cell proximal branch, despite a slight relative depolarization in the non-participating cell. As will be documented in Fig. 5, almost all participating cells have large distal branch radii ($> 0.24 \mu\text{m}$), while most non-participating cells have small distal branch radius ($0.15 \mu\text{m}$). Spikes in the larger branches generate larger membrane currents, which in turn lead to larger depolarizations beyond the branch point on the axonal trunk: compare, for example, the different attenuations at the branch point between a participating and a non-participating cell (Fig. 3B). The larger action potentials in the main branch, for participating cells, will in turn lead to larger spikelets in the respective proximal branches.
- iv. Somatic participation follows upon a proximal branch action potential; at the mid-branch site illustrated in Fig. 3, one sees a slight pause between a preceding spikelet and the full branch action potential. This pause occurs because the branch spike is actually initiated at the distal tip of the proximal branch. No proximal branch action potential occurs in the non-participating cell, presumably because the spikelets there are too small.

The inset in Fig. 3 shows the steady-state current–voltage relation for a compartment in the proximal axon. Note that there is a stable minimum at $\sim -60 \text{ mV}$, and an inward current does not appear (at steady-state) until $\sim -40 \text{ mV}$, a voltage well-depolarized compared to the amplitude of spikelets in the axonal branch. Because similar membrane depolarizations (in the branch) sometimes do and sometimes do not lead to an action potential, then the initiation of a full action potential in the branch must depend on transient fluctuations in local membrane properties (i.e. the membrane is not at steady-state); one possible relevant membrane property would be a transient increase in membrane impedance, as caused by closure of K^+ channels.

Action potentials in the proximal axonal branch of participating cells can be preceded by a small hyperpolarization

Why does the action potential in a participating cell's axonal branch occur when it does? Fig. 4A shows details of the initiation of the spike in the participating cell. It illustrates the voltage at the distal tip of the proximal branch; the action potential itself is truncated. Note that this spike was initiated from a hyperpolarization (arrow), in a region where (in the model) T-type Ca^{2+} channels were not present. A similar phenomenon was found in a

different simulation as well. A possible explanation comes from the kinetics of two relevant currents around resting potential (Fig. 4B). Slight hyperpolarization from ~ -60 mV reduces the already small value of g_{Na} , but also reduces $g_{K(A)}$. The latter will act to increase membrane impedance, so that a small transient depolarization may be able to set off a spike. Note that the width of the axonal spikelets (<1 ms, measured from -60 mV onset to -60 mV offset) is similar to the activation time constant of $g_{K(A)}$, also ~ 1 ms around -60 mV (Fig. 1A); we propose that the similarity of these time scales sets the stage for some spikelets setting off full action potentials while others do not. See also the Discussion for further comments on the apparent (but only apparent) contradiction of this result with earlier data of Debanne et al. (1997) and Kopysova and Debanne (1998).

Almost all participating cells have a large-radius distal branch, explaining the large-amplitude spikelets more proximally

In the model, a major factor in determining axonal branch spikelet amplitude, and hence the possibility of participation, is the diameter of the distal axonal branch (on which are located the gap junctions, and where high-frequency firing occurs; Fig. 2). Fig. 5 illustrates this. On the left is a raster plot of somatic action potentials during a simulated SPW-R (as in Fig. 2). Note that participation was almost completely restricted to pyramidal cell nos 1,...,1000; during the SPW-R illustrated, 59 out of 62 participating cells were from population nos 1,...,1000. As the right side of Fig. 5 shows, there was a discontinuity in distal branch diameter across the population, with this diameter small for cell nos 1001,...,4000 and larger for cell nos 1,...,1000. Furthermore, with the 'low-numbered' cells, branch diameter was larger for the lowest-numbered cells, and these were the cells firing the most. The physical reason is simply that, with larger branch diameter, there is less attenuation of spikes as they propagate from the distal branch into the main axonal trunk (Fig. 3B), in turn leading to larger spikelets in the proximal branch. That a few neuronal somata, wherein the distal branch is small, may fire is not surprising, given the nonhomogeneities in other parameters besides branch diameter (see Materials and Methods).

Small increases in transient axonal g_K can turn participating cells into non-participating cells

It was technically difficult to sort out systematic effects of varying $g_{K(A)}$ between neurons during a given simulation. We therefore compared two simulations, in which $g_{K(A)}$ density in the neurons of one simulation was scaled up (or down) relative to the same neurons in the other simulation. This comparison could, in principle, be compared to experimental data in which $g_{K(A)}$ is altered throughout the tissue by bath application of a drug. In the case of Fig. 6, we repeated the simulation of Fig. 2, only with $g_{K(A)}$ density increased along the main axonal shaft by $\sim 5\%$. Although spikelet amplitudes were not noticeably different, and resting membrane potentials were virtually identical, this alteration was sufficient to prevent spike initiation in the proximal axonal branch illustrated and it was sufficient to drastically reduce somatic participation overall (Fig. 6 inset).

Conversely, reduction in transient axonal g_K is predicted to lead to somatic bursts during SPW-R

We next examined the effects of 12.5% and 25% decreases in $g_{K(A)}$ density along the pyramidal cell axonal shafts. As Fig. 7 shows, a 25% decrease in $g_{K(A)}$ density caused distal branch spikes to induce larger partial spikes in the mid-axonal shafts (Fig. 7, bottom traces), inducing larger spikelets and more frequent action potentials in the proximal branches (not shown), and bursts of action potentials in cell somata. Fields and somatic participation were greatly increased (Fig. 7, upper two sets of traces). Not unexpectedly, a 12.5% decrease in $g_{K(A)}$ density (not shown) produced an intermediate situation, with increases in field amplitude and somatic firing compared to the control situation, but not as pronounced as for

a 25% decrease. This model prediction concerning the expected effects of 4-aminopyridine, a blocker of $g_{K(A)}$, to stratum oriens during SPW-Rs, may be experimentally testable.

Blockade of axonal $g_{K(M)}$ is predicted to cause somatic bursting in some participating cells

The 'M' type of K^+ conductance (blocked by muscarinic receptors, activating near rest, non-inactivating) is present in pyramidal cell axons (Pan et al., 2006). We have presented experimental and simulation evidence that axonal M-current is important in determining the period of kainate-induced beta2 (~25 Hz) oscillations in deep cortical pyramidal cells *in vitro* (Roopun et al., 2006), and also simulation evidence that this current might help to regulate very fast oscillations (>80 Hz) in neocortex (M.O. Cunningham et al., unpublished data). We therefore examined the effect of suppressing axonal M-conductance in the present SPW-R model (Fig. 8). This manipulation could lead to somatic bursting in at least some neurons (bottom traces in Fig. 8) but not others (Fig. 8, inset), and overall the effects on somatic participation were surprisingly small: 240 pyramidal cells participated in a total of three SPW-Rs in control conditions vs. 234 cells when axonal $g_{K(M)}$ was blocked.

There is strong overlap between cells participating during simulated theta/gamma and cells participating during simulated SPW-R, in the same model

During spatial exploration in a rodent, with its correlated hippocampal theta/gamma EEG state (and very fast oscillations; Colgin et al., 2009), a subset of hippocampal pyramidal cell somata discharge action potentials: place-cell firing; then, during awake immobility and slow-wave sleep, with their associated sharp wave/ripple complexes (Buzsáki, 1986; Buzsáki et al., 1992; Ylinen et al., 1995), many of the same pyramidal cell somata fire again, even with some tendency to recapitulate the temporal order of exploration-associated firing (reviewed in Carr et al., 2011). Why should this be? To suggest an hypothesis, we produced a simulation (Fig. 9) in which there was first a theta/gamma/VFO phase (with VFO present in the axonal firing and in synaptic currents; not shown) and then a subsequent phase of SPW-Rs. Of note are two features: first, as described above and observed experimentally (Bähner et al., 2011; Papatheodoropoulos, 2008), somatic action potentials are antidromic. In addition, somatic action potentials during theta/gamma are also antidromic, as would be expected from their axonal origin in this model (bottom traces in Fig. 9). This observation is consistent with a previous model of persistent gamma *in vitro* (Traub et al., 2000), and with the observations of spikelets during gamma *in vitro* (Fisahn et al., 2004), as well as in hippocampal pyramidal cells during exploration *in vivo* (Epsztein et al., 2010). Second, again consistent with previous models (Traub et al., 2000; Traub & Bibbig, 2000), axonal firing occurs at much faster frequencies than somatic firing, both during theta/gamma and during SPW-Rs: an experimentally testable prediction.

Interestingly, there was a strong overlap between cells somatically firing during simulated theta/gamma and simulated SPW-Rs, in Fig. 9. For example, there were 171 cells in common between the 189 firing during the theta/gamma epoch and the 246 firing during the second SPW-R, this out of a total of 4,000 pyramidal cells. If we picked 246 cells at random (with replacement), the expected number belonging to a defined subset of 189 would be $246 \times 189/4000 = 11$. A more careful calculation, allowing for non-replacement, indicates an expected overlap of 24 cells, still far fewer than the observed 171. Nevertheless, the strong overlap in firing populations is not truly surprising (in the model) because somatic firing is initiated in the same way during theta/gamma as during SPW-Rs, from the propagation of distal branch axonal spikes into the more proximal axon and branches, with consequent filtering. The same structural factors that favor somatic firing in one state will favor somatic firing in the other state and, at least in this model, those structural factors exist in the axons.

Discussion

Motivation for this study

Traub & Bibbig (2000) published a model of SPW-Rs, based on the hypothesis of electrical coupling between axons of pyramidal cells, that could account for many of the experimental observations known at that time: the occurrence of rippling itself in the field, ripple-frequency inhibitory postsynaptic potentials (IPSPs) in pyramidal cells, and infrequent somatic action potentials. The model predicted the occurrence of ripple-frequency excitatory postsynaptic currents (EPSCs) in interneurons and pyramidal cells, recently verified (Böhner et al., 2011, Maier et al., 2011); the model also predicted the antidromic nature of those somatic action potentials which did occur, also experimentally verified *in vitro* (Papatheodoropoulos, 2008; Böhner et al., 2011). The model neurons in the previous study had an unbranched axon and postulated the existence of a gap junction on the axonal trunk, consistent with dye-coupling data in CA1 pyramidal cells ($n = 4$; Schmitz et al., 2001). As a result of this construction in the Traub & Bibbig (2000) model, the electrically coupled network of axons would generate, as a population, ~200-Hz oscillations; axonal action potentials in a particular neuron, which did not fully invade the respective soma as antidromic spikes, could instead elicit spikelets. The reason why some axonal spikes invade the soma as full action potentials while others conducted decrementally to produce only spikelets, was this: the soma and dendrites impose a large impedance load on the axon, and g_{Na} density is also lower in the soma and dendrites than the axon. Hence, antidromic invasion involves crossing a region of 'low safety factor', and the invasion will be sensitive to membrane potential in the perisomatic region as well as to the membrane impedance, the latter in flux because of K^+ currents and synaptic inhibition. The occurrence of somatic spikelets under conditions of axonal activity, in our earlier model, also appeared consistent with *in vitro* experimental results (Schmitz et al., 2001).

Recently, however, two new experimental observations on *in vitro* SPW-Rs came to light that were not consistent with the Traub–Bibbig model (Böhner et al., 2011): (i) a near-absolute partition of the pyramidal cell population into cells that 'participated' (fired somatic action potentials during at least some SPW-Rs) and cells that did not participate. Such a partition clearly could have functional implications; (ii) the extremely rare experimental observation of pyramidal cell somatic spikelets during SPW-Rs. In addition, SPW-Rs in most pyramidal cells were associated with large somatic hyperpolarizations, although this was straightforward to account for with perisomatic inhibition. We therefore sought to refine the Traub & Bibbig (2000) model, retaining the consistency with certain data (antidromic spikes, high-frequency synaptic currents in different cell types) while simultaneously being able to account for the newer observations. Following a suggestion of N. Spruston (personal communication) we began studying the possible effects of axonal branching.

While electrophysiological and ultrastructural evidence for gap junctions at axonal sites in hippocampus continues to accrue (Hamzei-Sichani et al., 2007, in prep.; Vivar et al., 2012), as yet there are no definitive images (to our knowledge) of gap junctions on the axons of CA1 pyramidal neurons. On the other hand, we are also not aware of alternative models which do not postulate electrical coupling between pyramidal cells that are able to account for the known electrophysiology. [Some other models, e.g. Memmesheimer (2010), can account for portions of the data.] Furthermore, the absence of morphological data on gap junctions cannot be taken as proof that the requisite gap junctions do not exist: gap junctions can be very small (<50 connexons) and hard to find (Rash et al., 2007), and gap junctions continue to be recognized at unexpected locations (Hamzei-Sichani et al., in prep.) Likewise, the persistence of low- Ca^{2+} -induced VFO in connexin36-knockout mice (Hormuzdi et al., 2001) does not disprove the gap junction hypothesis: putative axonal gap junctions could use some other connexin. For these reasons, we consider it useful to explore

models incorporating gap junctions provided they make testable predictions which can be falsified.

The present model is indeed consistent with the new experimental data. The model works basically because of just a few structural and functional properties: (i) very fast oscillations, in terms of rapid overshooting action potentials, are (or, at any rate, can be) generated by electrical coupling between small axonal branches; (ii) rapid trains of branch spikes propagate orthodromically to produce rapid sequences of synaptic currents, as observed experimentally, but (iii) antidromic propagation of the trains of action potentials is intermittent, due to a kind of filtering produced by the branching axon itself, so that somatic firing is limited and is restricted to certain cells.

The notion of axonal intermittency, possibly with information-processing implications, has a long history. The demonstration of intermittent axonal conduction (i.e. the inability of axons, or portions thereof, to transmit trains of action potentials with perfect fidelity) has a long history (Barron & Matthews, 1935; Chung et al., 1970; Grossman et al., 1973; Smith, 1983). (The counter-demonstration that, at least for certain cells in certain conditions, and with orthodromic conduction, axonal propagation into branches can be exquisitely reliable, is more recent: Popovic et al. (2011). For clear physical reasons (Goldstein & Rall, 1974), much of the interest has been in cases in which there is axonal branching (Bucher & Goaillard, 2011; Debanne, 2004; Debanne et al., 2011). An additional axonal property which has been experimentally investigated, and which has direct relevance to the present results, is $g_{K(A)}$ (Debanne et al., 1997). The conditions in the model and in the protocols used by Debanne and colleagues are somewhat different, however. Debanne et al. (1997), and the simulations of Kopysova & Debanne (1998), produced somatic hyperpolarizations of ~ 10 mV, lasting tens of ms: slow enough to influence inactivation of $g_{K(A)}$, with the expected removal of inactivation during hyperpolarization able to reduce axonal propagation. In our case, we looked at small hyperpolarizations in the axon itself, lasting just a few ms, with the expected decrease in $g_{K(A)}$ activation increasing the ability of axonal membrane to initiate spikes.

The problem analyzed here is somewhat different from the case of orthodromic propagation, concerning instead retrograde propagation of high-frequency firing that originates in branches. Many experimental studies of axonal propagation have dealt with the fate of action potentials propagating orthodromically from the soma; reasonably enough, as that is how 'normal' action potentials might typically propagate. In the case of SPW-Rs, however, at least *in vitro*, and also possibly of persistent gamma oscillations, many of the action potentials are originated somewhere in the axon. The present study is therefore somewhat unusual in examining what might happen downstream to high-frequency trains of spikes originating in, rather than propagating into, one axonal branch, and how such trains might be modified by events in a different axonal branch.

The main proposal of this paper is that a proximal axonal branch can act as a nonlinear filter that gates antidromic propagation from the more distal axon. The way that the present model generates high-frequency network oscillations in the first place, and consequent high-frequency synaptic currents in pyramidal cells and interneurons, is similar in basic principles to what was described in Traub & Bibbig (2000) and Traub et al. (1999). The distinguishing principles by which some pyramidal cells exhibit antidromic spikes superimposed on large IPSPs while other pyramidal cells exhibit the IPSP alone, can be described this way:

- i. During *in vitro* SPW-Rs, the large somatic IPSP results from summated inhibitory inputs from interneurons, which are in turn stimulated to fire by VFO in the pyramidal cell axonal plexus.

- ii. VFO is generated in the axonal plexus (on the distal branches in the present model; see Fig. 1B), far enough from perisomatic regions so that the VFO can continue despite the presence of such synaptic inhibition. For VFO to occur in this way, a requirement is that action potentials be able to cross from axon to axon; this requires that gap junction conductances be large enough, and also that the axonal membrane be sufficiently excitable. Both gap junction conductance and axonal excitability are subject to modulation. For example, CA1 pyramidal cell axon excitability is increased by GABA acting on GABA_A receptors (Traub et al., 2003; Böhner et al., 2011) tonically, rather than by phasic synaptic release, at least in certain experimental conditions.
- iii. VFO spikes originating in the distal branches are attenuated to partial spikes as they propagate into the main axonal trunks. The amount of attenuation of the trunk partial spikes depends on the diameter of the distal branch.
- iv. The attenuated trunk partial spikes can recover to full spikes and propagate orthodromically but in retrograde (antidromic) propagation the trunk partial spikes attenuate still further. Propagation of such attenuated spikes all the way to the soma leads to spikelets of minimal amplitude (a fraction of a mV). This accounts for the experimental failure to observe spikelets at the soma (Böhner et al., 2011).
- v. Trunk partial spikes also propagate into the proximal branch, as spikelets. If the trunk partial spikes are too small (e.g. if the distal branch is small), the resulting spikelets never activate an action potential in the proximal branch, and the soma has no chance of participating. If the resulting spikelets are large enough (as after some experimental manipulation, but not under typical *in vitro* conditions) then the proximal branch may fire repetitively, leading to a somatic burst. At intermediate amplitudes, the spikelets may on occasion lead to a full spike in the proximal branch and this then propagates to the soma.

The model is consistent with the known occurrence of high-frequency IPSPs during ripples *in vivo* (Ylinen et al., 1995) but is also consistent with the recent demonstration of high-frequency EPSPs and EPSCs (Böhner et al., 2011; Maier et al., 2011). Models lacking VFO generation in the axonal plexus would not account for the antidromic nature of somatic spikes during SPW-Rs. The model generates high-frequency synaptic currents in a perfectly straightforward way: one need only assume that spikes can propagate from axonal sites, where VFO is generated, to downstream regions containing presynaptic terminals. However, the ability of the model to produce antidromic spikes is, we believe, powerful. It is not clear how models of SPW-R without axonal generation of VFO could accomplish this. In addition, if the axonal plexus is what generates VFO then the axons must be communicating with one another, and it is not clear how this might be done except non-synaptically; this is also consistent with the experimental observations of VFO and SPW-Rs in low-calcium media and in media where one or another type of phasic synaptic transmission is blocked (Draguhn et al., 1998; Nimrich et al., 2005).

Specific predictions are: (i) correlation of somatic participation with axonal branch anatomy; (ii) higher frequency firing of axons, as compared to somata, during both persistent gamma oscillations and during SPW-Rs. In the model, the branch diameter for the distal axonal branch correlates directly with the ability of a pyramidal neuron to participate, i.e. to generate somatic spikes during a SPW-R. (The simple absence of a gap junction in the axon could also explain failure of participation of the respective neuron.) Of course, in the model most of the other parameters are held constant. This is not likely to be true in real neurons. Testing of this prediction, therefore, may require imaging of a number of axonal trees in real cells, during SPW-R, in such a way that (i) it can be determined where spikes are initiated in

the axonal tree, (ii) the requisite branch diameters can be measured, and (iii) somatic voltage can also be measured, so that it is possible to tell whether a cell participates or not.

The higher frequency of axonal firing, as compared with somatic firing, was observed in every model neuron examined except those neurons that lacked gap junctions. Of course, experimentally it is not known how many neurons actually lack gap junctions, but we expect that this prediction could be tested in a relatively straightforward way, provided that somatic and axonal sites can be recorded simultaneously, along with a field electrode to determine when SPW-Rs are occurring.

If somatic participation is determined by axonal properties, could there be plasticity of axonal anatomy and intrinsic properties? This question has been considered by Bucher and Goaillard (2011) and by D. Debanne and colleagues (Debanne, 2004; Debanne et al., 2011). The present model suggests various ‘system parameters’ that nature might use to encode information in axonal plexi: gap junction conductances, excitatory axonal GABA_A receptors, axonal branch diameters, g_{Na} distributions and $g_{K(A)}$ distributions. What remains for future research to determine is whether nature in fact stores information in axonal plexi in such ways and, if so, how storage can be accomplished, and read out, in a specific fashion.

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Abbreviations

EPSC	excitatory postsynaptic current
IPSP	inhibitory postsynaptic potential
OLM	oriens/lacunosum–moleculare
SPW-R	sharp wave/ripples
VFO	very fast oscillation(s)

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Fig. 1. Structure and properties of model axon

A. Kinetics of model A-current, m_8 (activation, black) and h_8 (inactivation, green) above; time constant (τ) for the activation variable in the middle; time constant (green) for the inactivation variable below. The A-current is proportional to Hodgkin-Huxley m^4h . Note that activation is roughly 100-fold faster than inactivation. **B.** Layout of the 24 axonal compartments, in two cells (see Methods). Gap junctions were located on the distal branch (*). Ectopic spikes could arise in the distal main trunk, or at the tip of the distal branch, in different simulations. As later figures show, spikes developing in the distal branch, from ectopic activity or through the gap junction, propagate differentially out the main trunk vs. antidromically into the soma. The reason for this is the complicated nonlinear filtering imposed by the structural and intrinsic properties of the proximal axon, including the proximal branch. The compartmental structure of the soma/dendrites was as in Traub et al. (1994). Synaptic outputs followed spikes in the distal branch. **C.** Action potentials were induced (in an isolated pyramidal neuron), first in the proximal branch (black), then in the distal branch (green). In this case, the proximal branch spike propagates to the soma, but not

the distal branch. The distal branch spike leads to a spikelet in the proximal branch, but almost no voltage deflection at the soma.

Fig. 2. Network model produces repeating SPW-Rs when ectopic spike frequency, and pyramidal cell gap junction conductances, are time-dependent

For 100 ms intervals, repeating every 900 ms, mean ectopic frequency jumped from 0 Hz to 1 Hz per axon, and simultaneously pyramidal cell gap junctions opened (as in lower trace in A). A. upper trace shows repeating SPW-Rs. B. Expanded view of one of the sharp waves, with field above, number of overshooting somatic spikes in the 4,000-pyramidal cell population, and somatic voltage of a participating cell. The inflected action potential is antidromic and arises out of a hyperpolarization (compare Böhner et al. (2011)). Left inset shows the cross-correlation, for one of the SPW-Rs, of the field with the signal representing the number of participating cells. Right inset shows high-frequency components to EPSCs and IPSCs in a single pyramidal cell during one of the SPW-Rs: compare Böhner et al. (2011) and Maier et al. (2011).

Fig. 3. Example differences in axonal behavior between a participating cell (A, left), and a non-participating cell (A, right)

Data are plotted from the same SPW-R simulation. Cell #11 participates (2nd trace, left), while cell #3998 does not (right). The distal axon branch for each cell exhibits comparable high frequency firing (bottom traces), generated by the gap junctional coupling between axonal branches (Fig. 1). However, axonal spikes are less attenuated by the time they propagate into the proximal branches, in cell #11 than cell #3998, even though the axon of cell #3998 is slightly depolarized. The reason for this is that the distal branch of cell #11 is larger than for cell #3998, so that more current is injected by a branch spike in the participating cell, into the axonal shaft (see B). One of the spikelets in cell #11, proximal branch, succeeds in evoking a full spike, that can then propagate to the soma, despite the IPSP at the soma. Inset shows the steady-state current voltage relation of a proximal axonal compartment: note the stable minimum at around -55 mV. To evoke a spike in the axon requires a transient fluctuation in membrane impedance and/or voltage (see Fig. 4). **B:** differential attenuation in spikes, on passing from the distal branch (red traces) into the main axon shaft (black traces). Participating cell above, non-participating cell below. For the participating cell, axon shaft potentials are all > -21 mV; for the non-participating cell, they range from -51 mV to -27 mV.

Fig. 4. Details of the propagated action potential in the participating cell of Fig. 3

A. The spike (*, truncated) is initiated at the tip of the proximal branch, as shown in this trace. It is preceded by a small hyperpolarization, originating in perisomatic inhibition. This suggests the possibility that axonal IPSPs might also be able to initiate axonal spikes, and somatic participation. **B.** Variables proportional to steady-state g_{Na} (red) and $g_{K(A)}$ (black) in the same axonal compartment. Note that small hyperpolarizations from around -60 mV reduce g_{Na} (which is already small at that potential), but also reduce $g_{K(A)}$ – which will increase membrane impedance and allow the next spikelet to produce a larger transient depolarization.

Fig. 5. Correlation of large distal axonal branch diameter with participation

Left: raster plot of pyramidal cell somatic firing during a simulated SPW-R. Almost all participation is amongst cells 1 – 1,000 (although not all of these cells participate). Right: distribution of distal branch radius in the pyramidal cell population: this radius is relatively large (nearly 0.25 μm) for cells 1 – 1,000, and small (0.15 μm) for the other cells. The larger branch radius, in the branch where the gap junction is located and where high-frequency firing occurs (Fig. 3), causes larger spikelets in the main trunk and proximal branch, allowing for the possibility of generating a more proximal action potential, one that can in turn propagate to the soma.

Fig. 6. Slight increases in axonal $g_{K(A)}$ density decrease participation, even though axonal spikelet amplitudes are not noticeably different

The control run is as in Figs. 3–5. The signals shown in red are from a repeat of this run with axonal $g_{K(A)}$ densities increased ~5% along the main shaft. In the example shown here, the proximal branch then fails to spike, and no action potential can propagate back to the middle shaft, and thence to the soma. Inset: overlay of signals for somatic participation in the two cases, control (black), increased $g_{K(A)}$ (red). Overall, <10 somatic spikes occurred simultaneously after this $g_{K(A)}$ increase, vs. peaks at >30 somata in the control run.

Fig. 7. Decreases in axonal $g_{K(A)}$ density increase participation and lead to bursts of spikes in the soma of some pyramidal neurons

The signals in black are from the control simulation of Fig. 2. The signals in red are from a repeat of this simulation, in which axonal $g_{K(A)}$ density was decreased approximately 25%. This leads to a slight tonic depolarization in the axon (bottom traces), to larger axonal spikes in the mid-axon (a region of low safety factor in the model), to bursts of somatic spikes, and to a vast increase in somatic participation.

Fig. 8. Block of axonal $g_{K(M)}$ produces bursts in some participating cells, but population effects are subtle

The black signals are from the simulation used in Fig. 2. The red signals are from a repeat simulation with axonal $g_{K(M)}$ blocked in pyramidal cells. The fields and somatic participation are similar (compare Fig. 2). The bottom traces show a burst of somatic spikes in a cell formerly generating a single spike; but other cells (inset) show little change in activity, other than a slightly larger spike afterdepolarization.

Fig. 9. Similar antidromic activities in simulated theta/gamma and SPW-Rs, with higher frequency axonal vs. somatic firing in each case

A. An epoch of theta/gamma followed by SPW/Rs was induced following “Protocol 2” (see Methods), with time-dependent drives to interneurons, ectopic rates and gap junction conductances. **B.** Expanded segments of theta/gamma (1), left, and SPW-R (2), right. Not all cells fire, but action potentials which occur in these model conditions are antidromic. Bottom traces show model prediction that axonal firing is more intense than somatic firing, in both theta/gamma and during SPW-Rs.