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Sustained rhythmic activity in gap-junctionally coupled networks of model neurons depends on the diameter of coupled dendrites

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Abstract

Gap junctions are known to be important for many network functions such as synchronization of activity and the generation of waves and oscillations. Gap junctions have also been proposed to be essential for the generation of early embryonic activity. We have previously shown that the amplitude of electrical signals propagating across gap-junctionally coupled passive cables is maximized at a unique diameter. This suggests that threshold-dependent signals may propagate through gap junctions for a finite range of diameters around this optimal value. Here we examine the diameter dependence of action potential propagation across model networks of dendro-dendritically coupled neurons. The neurons in these models have passive soma and dendrites and an action potential generating axon. We show that propagation of action potentials across gap junctions occurs only over a finite range of dendritic diameters and that propagation delay depends on this diameter. Additionally, in networks of gap-junctionally coupled neurons, rhythmic activity can emerge when closed loops (re-entrant paths) occur but again only for a finite range of dendrite diameters. The frequency of such rhythmic activity depends on the length of the path and the dendrite diameter. For large networks of randomly coupled neurons, we find that the re-entrant paths that underlie rhythmic activity also depend on dendrite diameter. These results underline the potential importance of dendrite diameter as a determinant of network activity in gap-junctionally coupled networks, such as network rhythms that are observed during early nervous system development.

Keywords

Model; gap junction; rhythms; coupling; networks; neuroanatomy

Introduction

Electrical coupling through gap junctions is thought to be important in the generation {Manor, 1997 #166; Skinner, 1999 #73; Traub, 2003 #87} and synchronization of network activity {Beierlein, 2000 #93; Migliore, 2005 #162; Pfeuty, 2003 #23; Kopell, 2004 #107}, wave propagation {Bernstein, 2006 #256; Lewis, 2000 #241} and determination of activity phase {Chow, 2000 #108; Bem, 2004 #113}. Gap junctions are prevalent in early developmental stages {Peinado, 1993 #52; Peinado, 1993 #53; Kandler, 1995 #54} and often essential for the generation of rhythmic patterns in the developing nervous system {Corlew, 2004 #279; Moody, 2005 #280; Minlebaev, 2007 #281; Saint-Amant, 2000 #284}. Propagation of action potentials

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through gap junctions has also been shown to be important for network activity underlying learning {Moss, 2005 #116}.

Electrical signal propagation depends on gap junction conductance, the properties of the coupled neurons {Pfeuty, 2003 #23; Nadim, 2006 #207; Bernstein, 2006 #256}, their anatomical characteristics and gap junction location {Keener, 1990 #112; Saraga, 2006 #288; Migliore, 2005 #162; Rabbah, 2005 #90}. In a recent theoretical study we showed that the attenuation of signals across gap junctions between two passive cables is non-monotonically dependent on the diameter of the cables {Nadim, 2006 #207}. This dependence generates a unique “optimal diameter” for which the post-junctional potential is maximal.

Here we explore the consequences of the presence of an optimal diameter for signal transmission between gap-junctionally coupled passive processes for active signal propagation and for the generation of sustained network activity. We first use anatomically simple model neurons, consisting of passive soma and dendrites and an excitable axon, to demonstrate the dependence of signal propagation through gap junctions on dendrite diameter. We show that post-junctional potentials result in an action potential only if the diameter of the coupled processes is within a limited range near the optimal diameter. Moreover, when action potentials propagate through the gap junction, the delay to the onset of a new action potential is also diameter dependent.

We then examine the effect of dendrite diameter in networks that are structurally capable of producing sustained periodic activity. These include a ring network, a ring network with an arc and large, sparsely coupled networks {Traub, 1995 #72; Traub, 1999 #26; Lewis, 2000 #241}. We show that sustained periodic activity (or re-entry as described by Lewis and Rinzel {, 2000 #241}), can be generated in these networks only for a limited range of dendritic diameters and that the frequency of the rhythmic network activity depends on both dendrite diameter and gap junction location. Furthermore, in large sparsely coupled networks, the kernel of oscillatory activity (the subset of neurons that form single or multiple closed paths for propagation) also depends on dendrite diameter. We only consider sustained activity in relatively simple networks of neurons with no active elements except for their action potential-generating axon. Nevertheless, our results indicate that the diameter of coupled processes can be an important parameter in the generation and propagation of activity in gap-junctionally coupled networks.

Methods

Four different models were used for the present study. In all cases the standard model neuron consisted of a spiking axon made of six compartments, each with length 100 μm and diameter 10 μm , connected to a passive soma with a surface area of $400\pi \mu\text{m}^2$. From the soma one or more passive dendrites of length 600 μm emerged, each compartmentalized into six, 100 μm -long segments. The diameter (d) of these passive dendrites was the main parameter that was varied in the different simulation runs. All passive compartments were built with a specific membrane resistivity $R_m = 40 \text{ k}\Omega\text{cm}^2$, specific axial resistivity $R_i = 100 \Omega\text{cm}$, and specific membrane capacitance $C_m = 1 \mu\text{F}/\text{cm}^2$. These parameters of neuronal anatomy and membrane properties have been chosen in accordance to those used in our previous study {Nadim, 2006 #264}.

The membrane voltage of each axon compartment was determined by a simplified model of the standard Hodgkin-Huxley equations {Hodgkin, 1952 #44}, with the following steady-state activation, inactivation and kinetic terms.

$$\begin{aligned}
 m_{\infty}(V_m) &= \frac{1}{1 + e^{\frac{-(V_m+40)}{9}}} & \tau_m(V_m) &= 0(\text{Instantaneous activation}) \\
 h_{\infty}(V_m) &= \frac{1}{1 + e^{\frac{(V_m+62)}{10}}} & \tau_h(V_m) &= 1 + \frac{11}{1 + e^{\frac{(V_m+62)}{10}}} \\
 n_{\infty}(V_m) &= \frac{1}{1 + e^{\frac{-(V_m+53)}{16}}} & \tau_n(V_m) &= 1 + \frac{6}{1 + e^{\frac{(V_m+53)}{16}}}
 \end{aligned}$$

The maximal specific conductances of the different ionic currents in the axon was $G_{\text{leak}} = 25 \mu\text{S}/\text{cm}^2$, $G_K = 3 \text{ mS}/\text{cm}^2$, $G_{\text{Na}} = 15 \text{ mS}/\text{cm}^2$, with reversal potentials $E_{\text{leak}} = -54.3 \text{ mV}$, $E_K = -77.5 \text{ mV}$, $E_{\text{Na}} = +50 \text{ mV}$. When necessary, the voltage threshold for action potential generation was shifted by replacing V_m with $V_m - V_{\text{shift}}$ in all of the above equations simultaneously. The membrane and cable equations were numerically integrated utilizing the software Network using a fourth-order Runge-Kutta method with a time step of 10^{-6} sec (<http://stg.rutgers.edu/software/network.htm>). Smaller time steps did not change the output of the models.

Model 1

Two identical model neurons, each with a single dendrite emanating from the soma, were coupled by an electrical synapse (gap junction) with coupling resistance $R_c = 5 \times 10^7 \Omega$. The gap junction position was altered along the dendrite between segments 1 and 6 (Fig. 1A). To examine the effect of diameter, the diameter of both coupled dendrites was varied simultaneously with a step size of $0.1 \mu\text{m}$ over the range $0.5 - 14 \mu\text{m}$, while all other parameters remained fixed. An action potential was triggered in the distal compartment (to ensure successful action potential initiation independently of the passive load due to the dendrites) of the “presynaptic” axon (Fig. 1A) with a 2 nA , 2 msec long current pulse. To produce post-junctional action potentials in a reasonable range of dendrite diameters, the value of V_{shift} was set to 2 mV in this model. Note that changing the value of V_{shift} would result in a smaller or larger range of dendrite diameters for which a post-junctional action potential occurs but, so long as there is a post-junctional action potential, this parameter does not qualitatively change any of the results described.

For modeling uniformly tapered dendrites, the compartments of the dendrite cable structure were changed in diameter by linearly interpolating the diameter values between the diameters at the proximal and distal ends, with the distal end always set to $0.1 \mu\text{m}$ (Fig. 4 inset). The coupling axial conductances between two compartments were calculated according to the surface area and diameters of the coupled compartments.

Model 2

Two identical model neurons were built, each with six dendrites of different diameter emerging from the soma. The dendrite diameters were $0.5, 1, 2, 3, 4$ and $6 \mu\text{m}$, respectively. An electrical synapse ($R_c = 5 \times 10^8 \Omega$) connected the cells at the distal compartments between dendrites of identical diameter. The diameter of the coupled dendrites was varied by moving the gap junction from the thinnest to the thickest dendrites (Fig. 6A1), or by keeping all diameters fixed and varying only the diameter of the coupled postsynaptic dendrite (Fig. 6B1). In the presynaptic cell an action potential was triggered by applying a 5 nA , 2 msec long current pulse to the distal segment of the presynaptic axon. As in the case of Model 1, the value of V_{shift} was set to 2 mV in this model.

Model 3

Eight model neurons were arranged in a ring structure. All neurons were built with an axon, soma, and two $600 \mu\text{m}$ -long, passive dendrites. Adjacent neurons were coupled by a gap junction ($R_c = 4 \times 10^7 \Omega$) at the second dendritic segment, equivalent to a distance of $100 - 200 \mu\text{m}$ from the soma (Fig. 7A, schematic diagram). The diameter of all dendrites was varied

simultaneously from 1 to 14 μm . In order to initiate an action potential, a 3 nA, 2 msec current pulse was applied to the distal segment of the axon of cell A. In Model 3A, an inhibitory synapse modeled as an alpha-function was placed between the soma of cell A and the soma of cell H (Fig. 7A, top):

$$I_{syn} = g_{syn}\alpha(t - t_j)(V_{post} - E_{syn})$$

$$\alpha(t) = \frac{1}{\tau}\exp(1 - \frac{t}{\tau})$$

$E_{syn} = -70$ mV, $g_{syn} = 50$ nS, $\tau = 1$ msec, and the presynaptic threshold for activation (at times t_j) set to -20 mV. In the modified Model 3B, two cells were added to the ring structure to form an arc (Fig. 7B, top). Therefore, cell E was coupled to three, and cell G to four, identical cells. To account for the additional passive load compared to Model 1, the value of V_{shift} was set to 5 mV in this model, except when active dendrites were considered (see Results). In the case of active dendrites V_{shift} was set to 3.2 mV.

Model 4

Eighty identical model neurons, similar to those used in Model 3, but each with three dendrites emerging from the soma were randomly connected by a total of 112 electrical synapses (average of 2.8 gap junctions per cell) with $R_c = 3.3 \times 10^7 \Omega$ at position 2, thus 100–200 μm from the soma. The network was built as follows: randomly, two of the 80 neurons and one of the three dendrites of each neuron were selected. Only one gap junction per dendrite was allowed, restricting the maximal number of gap junctions to three for each cell. One cell in the network was stimulated three times by applying a 2 nA, 2 msec long current pulse to the middle segment of the axon, at a frequency of 33 Hz. Each simulation run lasted 1.5 sec. The diameter of the dendrites was varied simultaneously in steps of 0.5 μm from 1.5 μm to 4.5 μm . Simulation runs with larger diameters were performed as well, but for a diameter larger than or equal to 4 μm the action potential was never transmitted further than to the cells adjacent to the stimulated one and their neighbors.

The “kernel” of network activity is defined as the set of neurons that drives the periodic activity and is extracted as follows: based on the network connectivity, a graph G was constructed with each cell in the network represented by a node. Two nodes n_i and n_j are connected by a directed edge $n_i \rightarrow n_j$ if the two neurons are gap-junctionally coupled and if an action potential in cell n_j occurs within a time interval of 12 msec after cell n_i has fired, which corresponds to approximately the maximal propagation delay between two adjacent neurons in these networks. The resulting chain of neurons forming a closed loop is henceforth called the kernel of periodic network activity and was considered to be the putative pacemaker of the network. The resulting sub-network was visualized using the open source graph visualization software Graphviz (<http://www.graphviz.org/>). The kernels produced by this algorithm are unique for any given pattern of rhythmic network activity and are therefore useful for comparing network rhythms that may be similar in frequency but have a different underlying structure. Note, however, that the kernel produced by our algorithm does not necessarily produce the minimal set of neurons that are responsible for the sustained network activity. Although not minimal, the kernels of activity as defined in this study sufficiently describe the distinct pathways and patterns of activity depending on diameter or initiating neuron. However, a minimal kernel could be found as the subset of network neurons satisfying the following criteria: a) All neurons not included in the minimal kernel may be shut off (i.e. by setting the action potential-generating voltage-gated conductances to zero), but not necessarily removed, during the rhythmic activity without disrupting the rhythm or changing its frequency, b) Shutting off any neuron within the minimal kernel should disrupt the rhythm or change its frequency under the conditions described in a).

Ten different random network architectures were examined. Soma membrane potentials are shown in all cases.

Results

Action potential propagation between two coupled neurons depends on dendrite diameter

Previous modeling work has shown that a maximum amplitude post-junctional potential (i.e. minimal attenuation) exists for a unique diameter value of the coupled processes {Nadim, 2006 #207}. We will henceforth refer to this as the “optimal diameter”. The results of this previous study were obtained for passive cables under voltage clamp conditions of the proximal end of one cable. Although this study had predicted the existence of an optimal diameter for post-junctional potentials due to an action potential occurring in the “pre-junctional” cell, it did not directly examine the dependence of active propagation of signals on the diameter of coupled processes. To examine how the existence of an optimal diameter for passive signal transmission might affect transmission and propagation of an active signal, we began our study with the simplest architecture: two neurons electrically coupled along a passive dendrite (Fig. 1A).

The post-junctional voltage was measured in the soma of cell 2 (V_{2_s}) when two identical neurons were electrically coupled at specific locations along the dendrites (Fig. 1A; see Model 1 in Methods). Using the methods of Nadim and Golowasch {, 2006 #207} we calculated the passive signal propagation (assuming a passive axon) for this neuronal architecture when the two neurons were coupled at dendritic compartment 2. Thus we obtained a graph of normalized post-junctional potential (V_{2_s}/V_{1_s}) versus diameter that showed an optimal diameter for signal transmission at approximately 6.6 μm (Fig. 1B, black curve). This graph of post-junctional potential versus diameter is referred to as the “diameter tuning curve”. When an action potential was elicited in the axon of neuron 1, a finite range of diameters could be identified for which an action potential was generated in neuron 2; for diameters below or above this range, the action potential did not propagate into the post-junctional cell. Insets in Fig. 1B show the time course of V_{2_s} for different dendrite diameters. For diameters between 2.6 and 12.5 μm an action potential was generated in the first axonal segment of cell 2 and beyond. For diameters outside this range the pre-junctional action potential spread only passively to cell 2 (Fig. 1B, leftmost and rightmost insets).

If the location of the gap junction was changed to other dendritic compartments, action potential propagation was still limited to a small range of dendritic diameters, but this range varied with the gap junction location. This is shown in Fig. 1C where gray shading represents the range of diameters for which action potentials are generated in the post-junctional cell. When the dendrite diameter was $\leq 1.2 \mu\text{m}$ or $\geq 13.1 \mu\text{m}$ action potential propagation failed, no matter where the gap junction was located along the dendrite. With increasing distance of the gap junction from the soma, the range of diameters for which the action potential propagated to the postsynaptic cell became narrower.

Dendrite diameter not only affected the occurrence of a post-junctional action potential but also the delay to the onset of an action potential when it occurred. Figure 1D shows that the delay to fire an action potential also depends on dendrite diameter, with the shortest delay occurring near the optimal diameter (as determined by equations described in Nadim and Golowasch {, 2006 #207} and shown in Fig. 1B; compare, in this case, curve 2 in Fig. 1D with the tuning curve in Fig. 1B) for all gap junction positions. The optimal delay can also be seen in the onset of the post-junctional potentials shown in Figure 1B (superimposed in the inset of Fig. 1D).

Dependence of action potential propagation across a gap junction on membrane and gap junction parameters

To examine the effect of passive membrane parameters on the occurrence and the delay to the onset of a post-junctional action potential, we used the same setting as in Figure 1 (Model 1)

and varied the specific membrane (R_m) and axial (R_i) resistivity of the two coupled neurons. Increasing R_m resulted both in a broadening of the range of diameters for which there was action potential propagation across the gap junction and reduced the delay to the onset of action potentials in the post-junctional neuron at any given diameter (shown for coupling position 2 in Fig. 2A). However, the optimal diameter for the delay to the onset (as seen in Fig. 1D) showed little sensitivity to R_m and decreased only slightly as R_m was increased (Fig. 2B).

Decreasing R_i affected the range of diameters and delay to the onset of action potential propagation through the gap junction in a similar manner as increasing R_m (shown for coupling position 2 in Fig. 2C). However, there was an almost linear relationship between R_i and the optimal diameter for the delay to the onset (Fig. 2D).

Propagation of action potentials across the gap junction is, of course, quite sensitive to the gap junction resistance. As shown in Figure 3A for coupling at position 2 (see Fig. 1A), decreasing R_c drastically increased the range of dendrite diameters for which the post-junctional neuron produced an action potential and decreased the delay to the onset of the post-junctional action potential for any dendrite diameter. As in the case of R_i , the optimal diameter for the delay to the onset was almost linearly related to the value of R_c (Fig. 3B).

In many neurons, dendritic processes tend to taper toward the distal ends {Dunn, 1998 #294; Cuntz, 2007 #292; Desmond, 1984 #293}. To examine the effect of dendrite tapering on the propagation of action potentials across a gap junction we coupled two model neurons (Model 1) as in Figure 1, but each with a dendrite that uniformly tapered to a value of 0.1 μm at the distal end (Fig. 4 inset). The diameter of the proximal end of the dendrite was then varied and the effect on action potential propagation was examined. The results shown in Figure 4 indicate a similar effect as the uniform diameter shown in Figure 1. Changing the coupling position to more distal points of the dendrites decreased the range of (proximal) dendrite diameters for which action potentials propagated to the post-junctional neuron and, at any diameter for which propagation occurred, the onset delay of the post-junctional action potential was increased. Coupling at very distal positions (5 and 6) did allow a post-junctional action potential to be generated for any proximal diameter, presumably because of the extremely high axial resistance of these very thin dendrite compartments. For more proximal coupling positions, however, the range of dendrite diameters for which tapered dendrites allowed propagation to the post-junctional neuron was much larger than the comparable coupling position for a uniform-diameter dendrite (compare solid and dashed curves for coupling at position 2).

Many studies have shown that dendrites possess voltage-gated ion channels that can act to boost or shunt synaptic input currents {Bekkers, 2007 #289; Hausser, 2000 #290; Migliore, 2002 #291}. The effect of shunting on the post-junctional current is mostly accounted for by the dependence of the post-junctional action potential on R_m , as shown in Figure 2. To examine the effect of boosting currents on action potential propagation across a gap junction, we added the Hodgkin-Huxley voltage-gated sodium and potassium currents (present in the axon) to the dendrites but at a fraction of the axonal density (per unit area). Figure 5A demonstrates the effect, on the results of Fig. 1, of adding 10% of the axonal voltage-gated sodium and potassium current density. Although there is little qualitative change in action potential propagation across the gap junction as a result of making the dendrites active (compare Figs. 5A and 1D), it is clear that even this small amount of excitability in the dendrites can lead to dramatic boosting of propagation, especially for coupling at the distal portions of the dendrites. Consequently, there is much less difference in the effect of the position of the gap junction on the propagation of the action potential or its onset delay in the post-junctional neuron. Increasing the density of active currents in the dendrites beyond 10% had only a minimal effect on the propagation of action potentials in the post-junctional neuron (Fig. 5B shows a comparison for coupling at position 2).

Action potential propagation through a gap junction in neurons with multiple dendrites

The results shown so far indicate that signal transmission through a gap junction occurs for dendrite diameters near some optimal value and not for diameters above or below this range. The question remains, however, whether this optimal diameter range for signal transmission occurs only as a function of the growth of already-coupled dendrites or, instead by changing the gap junction position between dendrites of different but fixed diameters. Biologically this would imply the selection of coupling between already existing dendrites of fixed but different diameters (i.e. by insertion of gap junctions in those dendrites; Fig. 6A1) as opposed to the regulation of the diameters of a pair of coupled dendrites (i.e. by growing or shrinking the dendrites; Fig. 6B1) to achieve optimal signal transmission.

We addressed this question by examining whether an optimal diameter for signal transmission could be selected by changing the gap junction position between existing dendrites of fixed diameter. To test this we built two identical cells, each with six dendrites of different but fixed diameter, and a single gap junction was placed between the two cells at the end of homologous dendrites of identical diameter (Model 2, Fig. 6A1). The post-junctional potential was measured as a function of the diameter of the coupled dendrites. We found that the post-junctional potential monotonically increased as a function of this diameter and therefore there was no optimal diameter: for all diameters larger than a certain value, action potentials propagated through the gap junction (6 μm in Fig. 6A2). It was possible to change the diameter value above which action potentials propagated through the gap junction by changing the model parameters or the number of dendrites (not shown); but in all cases where action potential propagation occurred, it also occurred when the gap junction was moved to dendrites with larger diameter. We emphasize that in this protocol (as shown in Fig. 6A) the dendrite diameters are fixed and only the gap junction is moved among the existing (and homologous) dendrites. Thus, we conclude that if dendrite diameters are kept constant and only the position of the gap junction is changed among dendrites of different diameter, the largest-diameter dendrites always produced the best signal transfer (Fig. 6A2) and no optimal diameter is observed. This follows from the fact that the change in the diameter modifies the passive properties of the cell but moving the gap junction does not.

In contrast, if the position of the gap junction was fixed and the diameter of the coupled dendrite on the post-junctional side was varied (Fig. 6B1), a finite range of diameters was obtained for which action potential propagation was successful (Fig. 6B2). In this latter case, the time delay to the onset of an action potential was again minimized at a unique diameter (3 μm in Fig. 6B2 inset).

Sustained periodic firing depends on diameter in a network with ring architecture

Our results so far have shown that supra-threshold signal propagation through gap junctions can occur only if the diameters of the coupled dendrites fall within a finite range around an optimal diameter. The actual diameter range depends on the value of the threshold for signal generation (i.e. higher thresholds reduce the range of diameters that allows propagation). We examined the significance of this finding on network activity in a gap-junctionally coupled network by testing the hypothesis that sustained (as opposed to transient) activity in a gap-junctionally coupled network depends on the diameters of the coupled dendrites. We examined this hypothesis first in a ring network that is both simple in architecture and supports sustained activity.

A network with ring architecture was built by gap-junctionally coupling identical neurons to their immediate neighbor at the second segment of each of two dendrites (Model 3A, Fig. 7A, top). In a ring network, it is possible that an action potential initiated in one cell can propagate bi-directionally through the ring of neurons. Such action potentials, however, would collide at

a position opposite of the initiating cell due to the refractory period. To allow for sustained activity in the ring network the problem of bi-directional propagation must be overcome. This can be done, for example, by preventing one of the two neurons adjacent to the initiating neuron from firing. We addressed the problem by adding an inhibitory synapse from cell A, where action potentials are initiated, to cell H (Fig. 7A, top). This synapse effectively enforced unidirectional signal transmission and prevented the collision of the action potentials provided that the propagation delay along the ring was longer than the refractory period.

We found that, given the properties of the neurons in our model, a minimal ring network of eight neurons allowed signal propagation and that propagation depended on the diameter d of the coupled dendrites. Propagation was sustained and stable throughout the ring at diameters between 1.5 and 8.5 μm . At $d = 4 \mu\text{m}$ the spike frequency rapidly stabilized at 27.5 Hz (Fig. 7A, middle) whereas for $d = 7 \mu\text{m}$ the spike frequency was 22.8 Hz (Fig. 7A, bottom). As observed in Figures 1 and 2, the action potential propagation delay to an adjacent cell was minimized at a unique “optimal” dendrite diameter, and therefore the spike frequency in the ring network was also maximized at this unique diameter (Fig. 7C, solid symbols).

To demonstrate the presence of sustained network activity in a network built exclusively with electrical synapses, a different type of network architecture was used by adding two identical neurons to the ring structure: one to form an arc between neurons E and G and another to produce a branch emanating from neuron G (Fig. 7B, top). This added asymmetry in the network had an effect similar to that of the inhibitory synapse described above, because action potential propagation was blocked in one direction due to the higher conductance load of neuron G, now coupled to four neighbors rather than two. After initiation in cell A, the action potential propagated to cells B and H but the current density in cell G was insufficient to trigger an action potential, blocking counterclockwise propagation at that point. Consequently, the signal was only transmitted clockwise, and the simultaneous activation of the cells F and I provided enough current to initiate an action potential in cell G. With this somewhat more complex architecture again we observed that action potential propagation could be permanently sustained in a diameter-dependent fashion. For dendrite diameters between 1.7 and 2.3 μm sustained activity at 20.0 Hz was achieved (Fig. 7B, middle) while action potential propagation failed outside this range (Fig. 7B, bottom). Note that when sustained activity was present in this network, different delay times were observed between neurons with different conductance loads (e.g. cells D to E, E to F/I and F/I to G). The network frequency did not show a local maximum value with this architecture but the frequency values closely matched those of the ring-with-synapse architecture (Fig. 7C).

We examined the effect of active dendritic properties on sustained activity in the ring network by adding 10% or 20% (density per unit area) of the axonal voltage-gated conductances to the dendrites (as in Fig. 5). In both cases, the dendritic excitability led to: a) no propagation for large diameters, b) stimulus-independent oscillations for small dendritic diameters, and c) collision of action potentials moving in both directions around the ring for mid-range diameters. The first result (a) was expected, but the other two results (b and c, not shown) would not allow for a direct comparison of active and passive dendrites. It was possible to alleviate (c) by increasing the strength of the inhibitory synapse from cell A to cell H but the problem of spontaneous activity at small dendritic diameters (b) remained. To allow for a direct comparison between passive and active dendrites without changing too many parameters, we increased the threshold for action potential generation for the active-dendrite cases by setting V_{shift} to 3.2 mV (see Methods).

Figure 7D shows a comparison between the 10% and 20% active dendritic properties with the case of passive dendrites (0%, also with V_{shift} set to 3.2 mV; note that the increased threshold value compared to that used to generate Fig. 7C reduces the range of diameters that allow the

generation of sustained activity) for the ring network depicted in Fig. 7A. The active dendritic properties resulted in a larger range of dendrite diameters for which there was sustained network activity, despite the higher threshold for action-potential generation. (In fact, the range of diameters with 10% or 20% active properties were even higher than the passive case with lower action potential threshold shown in Fig. 7C.) Additionally, for any given diameter, the network frequency was higher with active dendritic properties. Although neither of these results is unexpected, they both point to the potential importance of active dendritic properties in boosting the ability of the gap-junctionally coupled network in producing sustained activity and in tuning its output frequency.

Adding 10% active properties to the dendrites also increased the range of diameters for which the ring with arc (Fig. 7B) produced sustained activity and, for any of these dendrite diameters, increased the frequency of network frequency compared to the passive case (not shown). However, with 20% active properties this network did not produce sustained activity because action potentials also back-propagated in the counterclockwise direction, despite the load on cell G, and resulted in collision.

Activity in randomly-coupled networks depends on the diameter of the coupled dendrites

To explore the effect of diameter in larger and more biologically realistic networks we examined the dependence of sustained activity on dendrite diameter in a large network of electrically-coupled neurons with sparse and random connectivity. A network of 80 neurons was randomly connected by gap junctions (Model 4; see Methods). These networks had $1.1 \pm 1.2\%$ (mean $\pm$ stdev) cells with one gap junction, $17.8 \pm 2.3\%$ with two, and $81.1 \pm 0.4\%$ with three gap junctions ($n = 10$ simulated networks). The presence of sustained network activity was examined by triggering a short train of three action potentials in a single cell. All networks analyzed generated sustained rhythmic activity but, as demonstrated above for simpler networks, their generation depended strictly on the diameter of the coupled dendrites. We observed sustained rhythmic activity only for dendrite diameters within the range of 2.0 to 3.5 μm .

The connectivity matrix diagram of one such network is shown in Figure 8A (black squares denote the presence of an electrical synapse). Figure 8B shows the firing times of the 80 neurons with dendrite diameters at 3 μm ordered according to the time of action potential generation after the initial transient interval. The average soma membrane potential for this network is shown in Figure 8D (middle). Stable and sustained spiking activity at 16.5 Hz was reached approximately 200 msec after the end of the stimulus train. Once rhythmic activity was established, all cells fired in the same order and with the same frequency (Fig. 8B). This network could also sustain periodic activity for a dendrite diameter of 3.5 μm with a frequency of 17.1 Hz (data not shown). When d was less than 2 μm (e.g. Fig. 8D, top) or larger than 3.5 μm (e.g. Fig. 8D, bottom) the action potential propagated no further than to the cells immediately adjacent to the initiating cell and died out soon after the last stimulus.

A randomly connected network can generate sustained periodic activity if it contains at least one ring-like structure (such as those in Fig. 7) along which action potentials can propagate unidirectionally. We used a detection algorithm (see Methods) to extract the cyclic structure underlying sustained activity which we refer to as the “kernel” of network activity. The sub-network that serves as the network kernel drives the entire network as activity spreads from the ring-like pacemaker structure to all other coupled cells. The time needed for activity to loop through this sub-network determines the frequency of network activity. For the networks examined here, this frequency ranged from 11.1 Hz to 19.3 Hz. The kernel of activity of the network in Fig. 8A with dendrite diameters of 3 μm , is shown in Fig. 8C.

We observed that the order of activation of the neurons could also depend on dendrite diameter since in most cases the path of activation varied with dendrite diameter. An example is shown in Figure 9 for a randomly connected network (connectivity shown in Figs. 5A and B, top right) in which the firing order differed greatly between cells with $d = 3.5 \mu\text{m}$ (Fig. 9A, left) and those with $d = 2 \mu\text{m}$ (Fig. 9B, left), despite identical connectivity (top, right corners). The kernel of network activity is shown in the bottom right diagrams of Figures 9A and 9B, demonstrating that an overlapping but not identical set of neurons participate in the generation of activity. Furthermore, the frequency of network activity was also dependent on dendrite diameter. For $d = 3.5 \mu\text{m}$ (Fig. 9A) the frequency was 17.8 Hz, while for $d = 2 \mu\text{m}$ (Fig. 9B), the frequency was 13.4 Hz.

Finally, sustained rhythmic activity could not be generated from every cell in the network as the starting point. We chose four networks to run separate simulations using each one of the 80 neurons as starting points and found that $31.3 \pm 7.0 \%$ of the cells (18, 23, 29 and 30 of 80 in the four networks) could induce sustained rhythmic activity. Again, when sustained rhythmic activity was generated, it was observed only for dendrite diameters within the range of 2.0 to $3.5 \mu\text{m}$.

Our goal in this study was not to explore all possible network parameters and architectures required for producing sustained activity, rather to demonstrate the dependence of sustained activity on dendrite diameter. Thus, we did not attempt to dissect out the minimum network size required to produce sustained periodic activity. Nevertheless, Figure 7A provided the minimum network size required for sustained activity with the given architectures and neuronal parameters. For networks with three dendrites such as those of Model 4 and the connectivity density we used, we have observed that approximately 50 randomly-connected neurons produce a lower limit.

Discussion

In a previous study we showed that signal transmission between gap-junctionally coupled, cable-like processes such as dendrites or axons is largest at a unique “optimal diameter” {Nadim, 2006 #207} and suggested, therefore, that the diameter of coupled dendrites can affect active signal propagation. Here we used computational modeling to confirm this hypothesis and establish that 1) action potentials may propagate to a post-junctional neuron only if the diameters of the coupled processes are within a finite range around the optimal diameter; 2) networks of dendro-dendritically coupled neurons can produce sustained periodic activity for a finite range of dendrite diameters; 3) the diameter of coupled dendrites affects the action potential propagation delay between the coupled neurons; and 4) the diameter of coupled dendrites affects the neuronal firing sequence within large sparsely-coupled networks thus defining a propagation path through the network. When sustained activity appears in such networks, this sequence forms a loop or re-entrant path {Lewis, 2000 #241}. The length of this loop, together with the dendrite diameter, determines the frequency of periodic network activity.

The importance of the role of dendrite diameter on signal propagation is at present not easy to understand. There is no known experimental method to regulate dendrite diameter and it is not known if dendrite diameter is an endogenously regulated cellular feature. However, just like branch point {Charych, 2006 #335} and dendritic spine number and length {Tada, 2006 #336} are regulated, it is conceivable that dendrite diameter is also regulated. In this case, it is possible that dendrite diameters could be regulated to match the optimal value to maximize propagation speed, network oscillation frequency, stability of network oscillations or other specific features relevant to the function of a particular neuronal network.

We observe that introducing tapering or adding a low level of excitability to the dendrites has the effect of greatly broadening the range of dendrite diameters over which action potential propagation across gap junctions can occur. Furthermore, both of these properties have the added effect of reducing the delay of signal propagation. This is particularly dramatic when adding active conductances to the dendrites, which allows the frequency of oscillations in networks with re-entrant paths, such as our Model 3, to be modulated over a large range (as seen in Fig. 7D). It can be assumed that adding different ionic currents or varying their parameters can greatly increase the degree to which oscillation frequency and diameter range can be regulated.

Although each of our results follows logically from the previous set of observations and ultimately from the presence of an optimal diameter between two passive gap-junctionally coupled cables {Nadim, 2006 #207}, the implications of these results are potentially widespread and many of the results are not immediately obvious. These include the presence of a unique diameter that determines a minimum propagation delay and therefore a maximum frequency of network oscillations in a ring network as well as the dependence of the oscillation kernels and frequency on dendrite diameter in complex networks. It is important to note that the effects observed as a function of diameter change are not present when other membrane parameters, such as membrane, axial and gap junction resistance, are varied because no other parameter results in optimal signal transmission across gap-junctions at a unique value {Nadim, 2006 #207}.

In this study we have examined relatively simple networks made of identical neurons with passive soma and dendrites. As such, our modeling study aims to point out the importance of dendrite diameter in signal propagation and the emergence of sustained activity in gap-junctionally coupled networks. Yet, even with the simplifications used in this study, periodic activity is generated over dendrite diameter ranges that are commensurate with those observed in gap-junctionally coupled biological neurons (cf. {Fukuda, 2003 #71}). Our goal here was not to fit parameters to match our results to any observed biological rhythm. Instead, it was to demonstrate a principle not yet proven to operate in any biological system. However, given that gap junctions have been proven to play a role in the generation of oscillatory activity in some systems {Manor, 1997 #166; Skinner, 1999 #73; Traub, 2003 #87}, particularly in early development {Saint-Amant, 2001 #25}, we emphasize the potential relevance of such a dendrite-dependent mechanism in the generation of rhythmic activity in networks of gap-junctionally coupled neurons.

Gap junctions are certainly not exclusively responsible for the generation of these rhythms {Traub, 2004 #210}. However, our results suggest that networks of gap-junctionally coupled neurons with simple geometry can, in principle, drive such oscillations (see also {Lewis, 2000 #241}) and that the frequencies of network activity may depend on the anatomical features of the coupled neurons. Previous studies have shown that sub-threshold network oscillations with similar frequencies as those observed in our study can be generated in gap-junctionally coupled networks independent of chemical synaptic connections {Manor, 1997 #166}. Thus, it appears that gap junctions can, in principle, constitute essential elements of rhythm-generating networks via multiple distinct mechanisms. This is supported by examples in which oscillations arise when chemical synaptic transmission has been reduced or eliminated {Angstadt, 1991 #103} and in developing nervous systems that display rhythmic activity before chemical synapses have been fully developed {Moody, 2005 #280; Minlebaev, 2007 #281} or in which chemical synapses seem to be unnecessary {Saint-Amant, 2000 #284; Saint-Amant, 2001 #285}.

An essential requirement for the generation of periodic sustained network activity in gap-junctionally coupled networks is that the network kernels (or re-entrant paths as defined and

applied by Lewis and Rinzel {, 2000 #241}) underlying the generation of rhythmicity are asymmetric. Such asymmetry can be achieved in many ways, including uneven distribution of chemical synapses, anatomical differences, distinct distribution of voltage-gated ion channels among the different neurons and distinct electrical coupling between the neurons. In our study (Model 4) asymmetry is obtained by the random electrical coupling of the neurons. In this case, extrinsic synaptic inputs might select different kernels of activity by introducing an additional degree of asymmetry to the network than the asymmetry conferred by the random gap junction coupling (see Fig. 7A for example). This would also affect the frequency of the network oscillations which is inversely related to the length of such pathways. Chemical synaptic interactions within the network, on the other hand, can affect properties of the individual neurons such as input resistance and neuronal polarization levels. Such intrinsic chemical synaptic effects can interact with gap-junctional effects. For example, changes in input resistance due to chemical inputs can change the diameter range and the optimal diameter value for signaling across gap junctions or chemical inputs may bring the neuron closer to threshold thus enabling gap-junctional currents to induce postsynaptic action potentials. Both of these effects will affect the propagation delay. Thus, chemical transmission within the network can contribute to network activity even when it is not essential for the generation of the activity patterns. Moreover, introducing sparse chemical synaptic inputs or low-frequency spontaneous firing activity in the neurons can increase the diversity of outputs generated by these gap-junctionally coupled networks. Just as the different “starting” neurons can activate different kernels and generate different sets of behaviors, brief perturbations to an ongoing rhythmic pattern due to localized chemical input could, in principle, dynamically reorganize the network and its activity patterns.

The presence of rhythmic activity in the nervous system during development is thought to play an important role in strengthening the chemical synaptic connectivity between neurons that display coherent activity {Zhang, 1998 #277; Peinado, 1993 #52; Kandler, 1995 #54; Moody, 2005 #280}. Such activity often occurs at a time when chemical synapses are being established {Corlew, 2004 #279; Moody, 2005 #280; Minlebaev, 2007 #281} or arises independently of chemical synaptic communication {Saint-Amant, 2000 #284; Saint-Amant, 2001 #285}. The generation of rhythmic activity in neurons that are passive (or weakly active) over most of their anatomical structure, yet have the ability to generate action potentials, may provide a simple mechanism that insures the propagation of activity waves known to be essential for the proper development of the nervous system {Moody, 2005 #270}. As chemical synaptic connections become more prevalent at later stages of development, the capacity to generate gap junction-based rhythmic activity may wane and eventually disappear altogether as neuronal growth and the changing input resistance of the cells move the optimal values away from the actual dendrite diameters. Our observations with our Model 2 also suggest that during development gap junctions are localized to particular dendrites.

The frequencies of rhythmic activity generated by randomly coupled networks under the conditions specified in this study fall within observed spinal cord (0.3 – 25 Hz) and brain oscillations (i.e. theta rhythms, 4–12 Hz and beta/gamma rhythm, 15–70 Hz) {LeBeau, 2005 #261; Traub, 2004 #210}. During development, rhythmic patterns of activity are normally slower than the patterns generated by the networks used in this study {Yvert, 2004 #287; Saint-Amant, 2000 #284; O’Donovan, 1987 #286}. We propose that at least two conditions inherent to the properties of our gap-junctionally coupled networks could generate such slow rhythms. One could simply be voltage-gated currents with large activation time constants that are responsible for the underlying oscillations. A second possibility arises from the fact that the range of diameters that permits signal transmission across the gap junction (as shown in Fig. 1B; also see Nadim and Golowasch {, 2006 #207}) depends on membrane conductance. As a result, the effective range of diameters for which the post-junctional potential leads to an action potential can be changed by membrane conductance changes. Thus, a slowly-accumulating

membrane conductance change can temporarily attenuate the signal and shift the effective diameter range away from the actual dendrite diameters and disrupt the sustained network activity. As this slow conductance deactivates when network activity is reduced, the dendrite diameters would again fall within the effective range and membrane conductance increase, and sustained activity can transiently resume. Episodic bursting activity would thus be generated.

In our model we have used gap junction coupling conductances that are large enough to produce a supra-threshold post-junctional potential. These values can be considered to represent coincident activation of multiple inputs. Amitai et al. {, 2002 #255} have shown that in large networks such as networks of inhibitory neurons in cortex, the average electrical coupling conductance is of the same order of magnitude as the leak conductance in these cells (~10 nS), which is within a factor of 2 of some of our models. Furthermore, Schmitz et al {, 2001 #92} and Moss et al {, 2005 #116} have shown that gap junctions between two neurons can allow for one-to-one action potential propagation. Thus, the generation of rhythmic activity based on action potential propagation in networks of purely gap-junctionally coupled neurons is entirely plausible, especially during early development when the neuronal input resistances are generally high {Cherubini, 1989 #276; Ramoa, 1994 #278}.

Conclusion

The primary accomplishment of this study was to demonstrate that dendrite diameter is an important parameter in action potential propagation through gap junctions. Although we provide some analysis of the recurrent rhythmic activity in networks that are randomly and sparsely coupled by gap junctions, our analysis is by no means exhaustive. The complex activities arising in large gap-junctionally coupled networks and the role of dendrite diameter as a parameter shaping rhythmicity and wave propagation in such networks need to be examined in much greater detail. Perhaps more importantly, the interaction between dendrite diameter-dependent signaling through gap junctions and chemical synaptic interactions needs to be properly investigated. Yet, our study shows that the anatomical structure of neurons in general and the size of the coupled processes in particular cannot be ignored when examining the role of gap junctions in network activity. This is particularly important in light of recent studies that show gap junctions to be much more prevalent in the nervous system than previously known.

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Figure 1. Effect of dendrite diameter and gap junction position on action potential propagation across a gap junction

A. Schematic diagram of the connected model neurons. The cells consist of a passive soma, a 600 μm long excitable axon, and a 600 μm long passive dendrite. The cells are coupled between equivalent dendritic segments by a single gap junction ($R_c = 5 \times 10^7 \Omega$). A current pulse is applied to the distal segment of the axon of cell 1 to elicit an action potential. **B.** The gap-junctional coupling ratio (ratio of soma membrane potentials measured after blocking the voltage-gated currents in the axons or calculated with equations in {Nadim, 2006 #207} for these cells when the axons are passive) as a function of dendrite diameter shows an optimal diameter for signal transfer when the two cells are coupled at dendrite segment 2. Insets show examples of the post-junctional response in the soma of cell 2 to an action potential generated in cell 1. The action potential propagates to cell 2 only for $2.6 \leq d \leq 12.5 \mu\text{m}$ (marked by dashed lines), with optimal diameter of 6.6 μm . **C.** Grey region denotes propagation of an action potential into the postsynaptic cell for different gap junction positions and indicated diameters. **D.** The delay to the onset of an action potential in the post-junctional soma with respect to the soma of cell 1 shown as a function of dendrite diameter. Each trace represents the delay for a specific position of the gap junction, indicated by the number at the right side of the trace. The minimum of each trace is marked by an 'x'. Inset shows the rise of the post-junctional potentials shown in panel B, demonstrating that the fastest rise time is near the optimal diameter shown in panel B.

Figure 2. Effect of passive dendrite membrane properties on the diameter dependence of action potential propagation across a gap junction

Model 1 as shown in Fig. 1A with identical parameters was used, except that R_m or R_i were modified. The gap junction was placed at position 2. **A.** Delay to the onset of an action potential in the post-junctional soma with respect to the soma of cell 1 shown as a function of dendrite diameter. Each trace represents the delay for a specific value of R_m . Values of R_m at or below 5 k $\Omega\cdot\text{cm}^2$ did not produce an action potential in the post-junctional neuron when the coupling was at position 2. **B.** The diameter at which the minimum delay occurs (optimal) is graphed as a function of R_m . **C.** Delay to the onset of an action potential measured as in A. Each trace represents the delay for a specific value of R_i . **D.** The diameter at which the minimum delay occurs is graphed as a function of R_i . Inset shows a schematic diagram of the connected model neurons. --> REMOVE!

Figure 3. Effect of gap junction resistance on diameter dependence of action potential propagation across a gap junction

Model 1 as shown in Fig. 1A with identical parameters was used, except that R_c was modified. The gap junction was placed at position 2. **A.** Delay to the onset of an action potential in the post-junctional soma with respect to the soma of cell 1 shown as a function of dendrite diameter. Each trace represents the delay for a specific value of R_m . **B.** The diameter at which the minimum delay occurs (optimal) is graphed as a function of R_c .

Figure 4. Effect of dendritic tapering on diameter dependence of action potential propagation across a gap junction

Model 1 was modified to have tapering dendrites all ending in 0.1 μm (inset diagram).

Otherwise, identical parameters as in Fig. 1 were used and each trace corresponds to a different gap junction position along the dendrite. Delay to the onset of an action potential in the post-junctional soma with respect to the soma of cell 1 is shown as a function of the diameter of the proximal end of the dendrite. When the gap junction is placed at the last two compartments no action potential transmission occurred with the parameters used. For comparison, the uniform-diameter dendrite model with gap junction coupling at position 2 is shown (from Fig. 1D, dashed red trace). Optimal diameter in each case is marked with a star.

Figure 5. Effect of dendrite excitability on diameter dependence of action potential propagation across a gap junction

Model 1 as shown in Fig. 1A with identical parameters was used except that voltage-gated ion channels (same as in the axon) were added to the dendrites. “% active” indicates fraction of maximal conductance density added to the dendrites relative to the axonal values. **A.** Delay to the onset of an action potential in the post-junctional soma with respect to the soma of cell 1 shown as a function of dendrite diameter when the gap junction was placed at different positions along the dendrite and dendrites had 10% active currents. **B.** Delay to the onset of an action potential as a function of dendrite diameter for different levels of active dendritic currents. Gap junction coupling is at position 2. Stars mark the optimal diameters for signal transmission.

Figure 6. Signal transmission through a gap junction in cells with multiple dendrites

A. The effect of changing the coupling position between existing pairs of dendrites of fixed (but different) diameters. **1.** Schematic diagram of the coupled model neurons. Arrows indicate the change in coupling position. Both cells consist of a passive soma, a 600 μm long excitable axon, and six 600 μm long passive dendrites with diameters 0.5, 1, 2, 3, 4, and 6 μm (top to bottom). The electrical synapse ($R_c = 10^8 \Omega$) connects one pair of dendrites of the same diameter in each simulation run. Action potentials were triggered at the distal point of the axon of one cell (marked on the left) and post-junctional potentials recorded from the soma of the second cell ($V_{2,s}$). **2.** Post-junctional potential measured in the soma of cell 2. The color denotes the dendrite diameter as in panel A. Only when the cells are coupled at the dendrite with the largest diameter ($d_6 = 6 \mu\text{m}$), the action potential propagates to the second cell and no optimal diameter exists. **B.** The effect of changing the diameter of the post-junctional dendrite (d_4) in the case shown in the middle panel of A1. **1.** Schematic diagram of the coupled model neurons. The diameter of the dendrite shown in red was modified. All other parameters remained unchanged and are as in A. **2.** If the cells are coupled at a given dendrite (d_4) and the diameter of only that particular post-junctional dendrite is varied, action potential propagation is successful for $2.5 \leq d_4 \leq 3.4 \mu\text{m}$. The threshold for action potential initiation was set $V_{shift} = 0.4 \text{ mV}$ lower than in A2. Inset shows the delay of the action potential in the post-junctional soma with respect to the presynaptic soma as a function of the post-junctional dendrite diameter.

Figure 7. Diameter dependence of self-sustained activity in a ring structure

A. Top: Schematic illustration of the ring architecture with a single chemical inhibitory synapse. Each neuron in the ring structure is made of an excitable axon, a passive soma, and two passive dendrites (see Model 3A in Methods). Dendrites were always connected at the second dendritic segment ($R_c = 4 \times 10^7 \Omega$), and the inhibitory synapse was placed between the soma of cell A and the soma of cell H. **Middle and Bottom:** Sequence and time of action potential firing in the network at two different diameters. **B. Top:** Schematic illustration of the ring architecture with an additional arc (see Model 3B in Methods). Neurons have two dendrites and are coupled as in panel A but for simplicity are shown as circles. **Middle:** Sequence and time of action potential firing in the network for $d = 2 \mu\text{m}$. **Bottom:** For $d = 1.5 \mu\text{m}$ network activity dies out. **C.** Frequency of network activity for cases shown in panels A and B, when activity is sustained. **D.** Frequency of network activity for the case shown in panel A, when the dendrites had 10% or 20% active currents. (“% active” indicates fraction of maximal conductance density added to the dendrites relative to the axonal values.) The passive case (0%) is added for comparison. V_{shift} is 3.2 mV in panel D and 5 mV in panels A–C (see text).

Figure 8. Diameter-dependence of activity in a network of 80 randomly coupled neurons
 Each neuron in the ring structure is made of an excitable axon, a passive soma, and three passive dendrites (see Model 4 in Methods). **A.** Connectivity diagram for an 80 cell network. A black square represents an electrical synapse between two cells. **B.** Raster plot of firing times of all 80 cells in the network after sorting. $d = 3 \mu\text{m}$. Periodic sustained activity stabilizes after ~ 200 msec. **C.** The kernel of sustained activity detected by the algorithm described in Methods. **D.** Average soma membrane potential for $d = 1.5, 3$ and $4.5 \mu\text{m}$. For $d = 1.5$ and $4.5 \mu\text{m}$ network activity is not sustained and all cells return to their resting potential shortly after the stimulus stops (stimulus indicated by vertical arrows under time axis).

Figure 9. Effect of dendrite diameter on firing sequence within a network of randomly coupled neurons

A. For dendrite diameter $d = 3.5 \mu\text{m}$ periodic network activity is sustained and all cells maintain the order of action potential firing at a frequency of 17.8 Hz. This is shown in the raster plot of firing times (top left; sorted in order of firing) and the average soma membrane potential (bottom left). Connectivity diagram for the network is shown on the top right. Black squares represent electrical synapses between cells. The kernel of network activity is shown on the bottom right. **B.** For dendrite diameter $d = 2 \mu\text{m}$ and the same coupling architecture (top right) as in panel A the network produced sustained periodic activity but with a different order of neuronal firing and at a different frequency (13.4 Hz). The different firing order can be seen in the raster plot of firing times plotted using the same ordering sequence as in panel A (top left). From the average soma membrane potential (bottom left) one can observe the difference

in frequency. The kernel of network activity (bottom right) indicates a different but overlapping subset of neurons compared to the activity shown in panel A: black cells are common to both kernels; red cells are new cells in kernel B that are not in kernel A; red arrows indicate new paths for propagation or a change in the direction of propagation; the blue cell is part of kernel A but drops out from kernel B.