TITLE:

Axial current reversal promotes synchronous correlation between dendritic membrane potentials during large scale synaptic input.

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ABSTRACT

We report two results from a simulation study of spatial temporal interactions in a dendritic tree during large scale synaptic input. The first is a feedback mechanism following individual synaptic inputs, which results in a reversal of the axial current 1-2 ms after activation of an input. The second is a time domain transfer function analysis between the membrane potential fluctuations at different sites, which has a symmetrical time domain structure indicative of a two way flow of axial current in the dendritic tree. These results may have implications for our understanding of synaptic integration.

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INTRODUCTION

Under conditions of large scale synaptic input, individual neurones in the central nervous system are acted on by several thousand inputs distributed over the dendritic tree (e.g. Holmes & Woody, 1989; Bernander et al., 1991; Rapp et al., 1992). The location and timing of individual synaptic inputs combine to produce the fluctuations of the membrane potential throughout the cell. These fluctuations have a random appearance and are larger in magnitude than individual inputs (Calvin & Stevens, 1968; Bernander et al., 1991). When there is sufficient excitation, these membrane potential fluctuations will ultimately act to modulate the timing of output spikes (Calvin & Stevens, 1968). Thus, variation in the output spike timings reflects membrane potential fluctuations throughout the cell, which in turn reflects spatial temporal interaction between large numbers of post synaptic potentials.

In this simulation study we are concerned with describing the process of spatial temporal interactions within a dendritic tree, to gain insight into how these might ultimately act to shape the output discharge of the neurone. We report here two new results related to spatial temporal interactions in a dendritic tree. The first is a feedback mechanism following individual synaptic inputs to a dendritic tree. The feedback is a result of a reversal of the axial current in either the distal or proximal direction, on the time scale of 1-2 ms. The second aspect is the relationship between membrane potential fluctuations during large scale synaptic input. We characterise these on a millisecond time scale using a statistical signal processing framework to estimate the system transfer function between the site of input and the somatic spike generating site. This analysis reveals the presence of a symmetrical time domain structure during large scale input. This we interpret as indicative of a continual two way flow of axial current between different sites in the dendritic tree, which may have implications for our understanding of the process of synaptic integration

METHODS

Model neurone: Description and parameters.

The model neurone is based on a class of cells with extensive dendrites, which are believed to be mainly passive, and whose morphology and electrophysiology have been widely studied, namely spinal motoneurones (Cullheim, Fleshman, Glenn & Burke, 1987; Fleshman, Segev & Burke, 1988; Rall, Burke, Holmes, Jack, Redman & Segev, 1992). The model is described in detail in Halliday (2000, 2001). Briefly, the cell consists of a spherical soma and 12 tapered dendrites, lengths 766 μm, 1258 μm and 1904 μm, which are equivalent to electrotonic lengths (in the absence of any inputs) of 0.7, 1.0 and 1.5 electrotonic units, the cell contain four of each. In the present study we consider two different scenarios for synaptic input. Firstly the effects of a single synaptic input, and secondly, the effects of large scale synaptic input. The single synaptic input is located in the centre compartment of a medium length dendrite, in passive electrotonic terms, this is 0.5 electrotonic units from the soma, on a dendrite of electrotonic length 1.0. We refer to this below as the mid-dendritic location. The large scale synaptic input simulates the typical operating regime for the cell, and is provided by 996 synaptic inputs, which are distributed between dendritic and somatic compartments uniformly by surface area. Each input fires at 32 spikes/sec with a random discharge pattern, generated using an exponential inter spike interval distribution, this simulates the background noise input to the neurone. This level of synaptic activity equates to an average excitation of 31,872 EPSPs/sec as input to the model neurone. In addition, we also use a combination of these two input regimes to study how a single input interacts with the background synaptic activation. During large scale synaptic input, the threshold and after hyperpolarisation components in the model are suppressed so that no output spikes are generated, this allows the spatial temporal interactions in the dendrites to be studied without contamination from these events.

Data analysis.

To describe the process of synaptic integration in a dendritic structure we propose to use a statistical signal processing framework, originally designed for analysis of stochastic neural data (Halliday et al., 1995). In this framework the membrane potential fluctuations are regarded as stationary stochastic time series and the spike

trains as realisations of stochastic point processes. We use estimates of the time domain transfer function to describe the relationship between dendritic and somatic membrane potential. The framework includes the facility for setting confidence limits on all parameter estimates, these provide a useful guide to assess the time scale over which the membrane potential fluctuations at the two sites are related. Full details are in Halliday et al (1995), and a software archive is available online at http://www.neurospec.org/.

RESULTS

The presence of a feedback mechanism in the dendritic tree following individual synaptic inputs is illustrated in figures 1 (solid lines). This shows the axial current flowing out of the mid dendritic compartment in the proximal and distal direction following a single synaptic input. The current flow in the proximal direction shows a rapid increase following the input, which peaks at 0.3 ms, followed by a slow decay back towards zero, and is entirely consistent with the mechanism of electrotonic spread of potential in one direction (Rall 1964, 1977). However, the axial current in the distal direction peaks at 0.25 ms, then has a reversal of direction after 0.9 ms, which reaches a peak at 1.55 ms, before decaying back to zero. Thus, following an individual synaptic input to the mid dendritic location, the current flows away from the site of input in both distal and proximal directions immediately after the input. A short time later, the current in the distal section of dendrite reverses direction and starts to flow in the proximal direction towards the soma. This reversal occurs in a time scale of under 1 ms, indicating that it is local and not reflective.

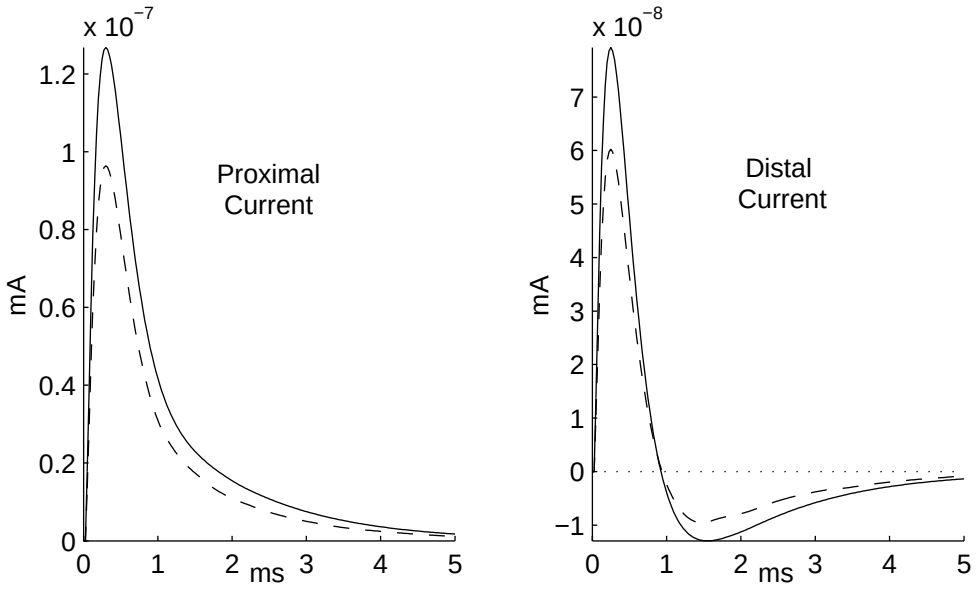

Figure 1. Axial membrane current, i_a, from the mid dendritic compartment to its proximal neighbour (left), and its distal neighbour (right), note the reversal of axial current after 0.9 ms. The solid lines indicate the current in response to a single synaptic input applied in isolation, the dashed lines are the current due to a single input in the presence of large scale background activation of the cell.

The normal operating regime for cells typically involves large scale synaptic input. To determine if the axial current reversal mechanism is present during the spatial temporal interactions which accompany large scale synaptic input we repeated the above analysis of i_a in the presence of large scale background synaptic activity. This was done in two stages. In the first stage the simulation was run with 996 synaptic inputs providing the background activity as described in the methods. In the second stage, the same 996 input spike trains were applied along with one additional extra synaptic input to the mid dendritic location. Figure 1 (dashed lines) illustrate the additional component of i_a in the proximal and distal direction, respectively, for the single synaptic input in the presence of the 996 background synaptic inputs. These traces represent only those components of i_a which result from the additional synaptic input over and above the 996 background inputs to the dendritic tree. They have the same general form as the solid lines, but are reduced in magnitude. One effect

of the large scale synaptic input is to depolarise the membrane potential towards the synaptic reversal potential (in this case from the resting potential of –70 mV to –55 mV). This increase in the membrane potential results in a reduction in the electrical gradient available to drive the ionic currents through the membrane, which can account for the reduction in the magnitude of i_a. Despite the additional background inputs, there is still a clear reversal of i_a following a synaptic input.

Figure 2 explores the relationship between the spike train input and the membrane potential fluctuations during a 100 second run with a single input applied to the mid dendritic input location which is activated by a spike train firing randomly at 32 spikes/sec. Figure 2 shows the system transfer function between the spike train input and the somatic membrane potential fluctuations, and the dendritic membrane potential fluctuations at the site of input and the somatic fluctuations. These figures are very similar in form, indeed the somatic membrane potential fluctuations are common to both estimates. That for the spike train input can be considered as an impulse response. It has the form expected from predictions of classical 1D cable theory (Rall 1964, 1977), with a rapid rise time and slower decay back towards zero, the upper 95% confidence limit is crossed at +41 ms. This value can be taken as an indication of the average span of dependency (in the statistical sense) of the effects of individual input spikes. The estimate using the membrane potential fluctuations as input is similar, in this case the upper 95% confidence limit is crossed at + 31 ms, however, in addition, there is a small component prior to time zero. This we suggest is due to the reversal of the axial current illustrated in figure 2. The section prior to zero lag cover the time scale 1-2 ms, which are consistent with the time scale over which the axial reversal occurs in fig 2.

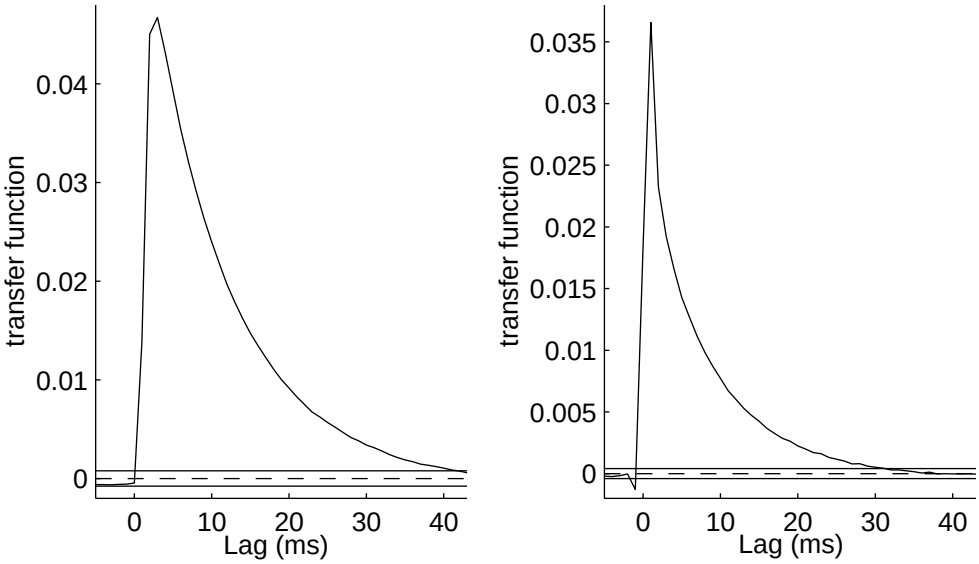

Figure 2. Estimate of time domain transfer function between Single spike train input to the mid dendritic location and the membrane potential fluctuations at the soma (left), and Membrane potential fluctuations at the input location and those at the soma (right). Both estimates are constructed from 100 seconds of data sampled at 1 ms intervals. The spike train has a mean rate of 32 spikes/sec, with an exponential distribution of intervals (coefficient of variation ≈ 1.0).In both plots the dashed horizontal lines are the null value for the estimate (zero), the sold horizontal lines are the upper and lower 95% confidence limits, under the assumption of two independent signals.

In addition to the above analysis, the overall pattern of i_a accompanying large scale synaptic input can be used to investigate any trends in the axial current during large scale input. Figure 3 (left) illustrates a 100 ms segment of i_a between the mid dendritic compartment and its proximal neighbour during the presence of the large scale synaptic input. Positive values of current indicate i_a flowing in a proximal direction, negative values indicate axial current flowing in the distal direction. The current continually fluctuates about zero resulting in frequent changes in the sign of the current. This process of current reversal can be usefully characterised using the sequence of times at which there is a change in the sign of the axial current. In a 10 second sample there

were a total of in 6338 reversals of i_a. The coefficient of variation (c.o.v.) for the sequence of time intervals between consecutive current reversals in this sequence was 0.98. This is very close to the expected value of 1.0 for a random sequence of events. The values for this analysis of i_a between the mid dendritic compartment and its distal neighbour were 5792 reversals, and a c.o.v. of 0.95. This analysis suggests that, under conditions of large scale synaptic activation, the timing of changes of direction of i_a in a dendritic tree is well modelled by a random process.

Figure 3 (right) illustrates the system transfer function between the membrane potential fluctuations in the mid dendritic location and those at the soma during the large scale input. This estimate is symmetrical in form, and is significant over the range –16 to +14 ms. The symmetrical form is indicative of a constant exchange of current between the two locations over a millisecond time scale during synaptic activation.

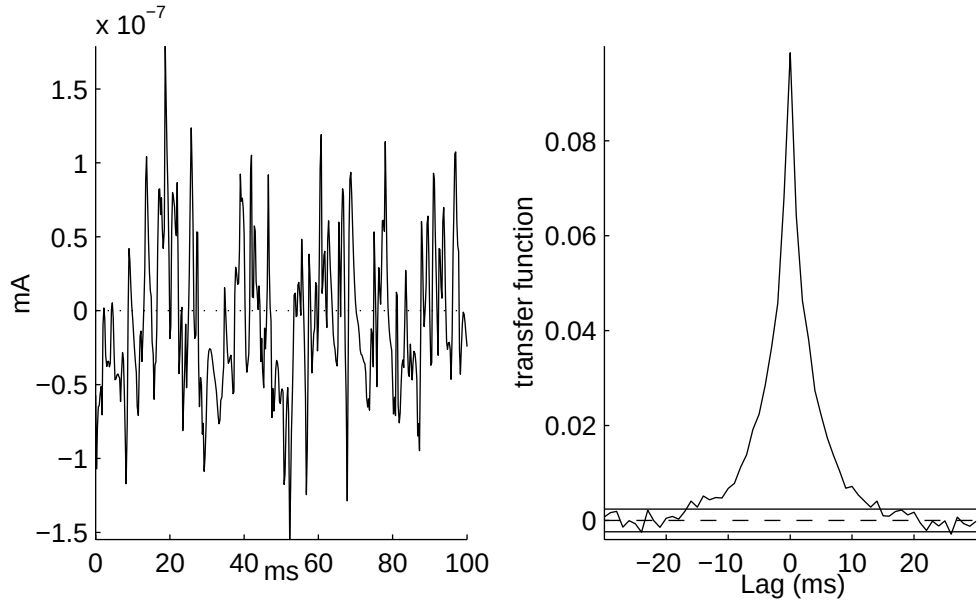

Figure 3. Section of 100ms duration showing axial current between the mid dendritic compartment and its proximal neighbour during large scale background activation of the neurone (left). Estimate of time domain transfer function between the membrane potential fluctuations at the mid dendritic location and those at the soma for a 100 s record during large scale synaptic input (right).

DISCUSSION

We have reported on two related mechanisms with the intention of gaining insight into the role of spatial temporal interactions in dendritic structures. In both cases we have revealed additional complexities are present in the integration of synaptic inputs within a dendritic structure. Single synaptic events, either in isolation or as part of large scale synaptic input, can be accompanied by a reversal of the axial current following individual synaptic inputs (Fig 1). Large scale synaptic input is accompanied by a constant two way flow of axial current between different parts of the dendrite, which results in a correlation structure between the membrane potential fluctuations (Fig 3).

Here we have reported a reversal of axial current only in the distal direction. This is due to the tapering of the dendrite in the distal direction. Our motoneurone model has a uniform taper of 0.5 μm reduction in the dendrite diameter per 100 μm increment of dendrite length, thus the input impedance will be greater in the distal direction than in the proximal direction. This is reflected theoretically in a smaller voltage transfer ratio looking in a proximal direction than in a distal direction (Nitzan et al., 1990; Jaffe & Carnvale, 1999). Simulations with a simplified dendritic structure consisting of a spherical soma attached to a uniform diameter dendrite of electrotonic length 1.0 have revealed that current reversal can occur in the proximal direction for inputs close to the soma, and in the distal direction for inputs further away from the soma, with a region in between where no

current reversal occurs (results not shown). Thus the process of current reversal appears to be intimately related to neurone geometry.

Our results in figures 2 and 3 are based on analysis of paired membrane potential fluctuations within a single model neurone. Experimental verification of the results of the present simulation studies therefore requires data from paired intracellular recordings from the same cell. Such data is available from the study of Buchanan and Kasicki (1999) who recorded from motoneurones during fictive swimming activity in the lamprey, with the aim of characterising the strength of shared input to pairs of motoneurones. As a control to establish the maximum strength of correlation to be expected, Buchanan and Kasicki made paired intracellular recordings from the same motoneurones. A cross correlation analysis (similar to our transfer function analysis) revealed a symmetrical correlation structure very similar to that reported here (Buchanan and Kasicki, 1999, fig 3A). Buchanan and Kasicki suggest that the differences in paired intracellular recordings from a single motoneurone may reflect differences in the spatial distributions of synaptic inputs to the cell. The present simulation results are broadly comparable with the results from their experiments.

The axial current reversal does not occur until 1 ms after activation of the input. Thus, there is not a distinct component in the resultant EPSP which can be attributed to the current reversal, which will instead act subtly to shape the form of the EPSP at the soma. Because of this, the system response with the spike train as input (Fig 2, left) is not sensitive to the presence of the feedback mechanism, however, the estimates with the mid dendritic membrane potential fluctuations as input signal (Fig 2, right) is sensitive to the relative timing of the i_a reversal, which appears as a small component at negative time lags.

For the large scale input, the system transfer function has a symmetrical form. It is likely that two mechanisms will contribute to this. The moment to moment variations in the timings and location of synaptic inputs will be the principal factor contributing to this pattern of interaction. In addition, the systematic reversal of i_a following individual synaptic inputs will contribute to the overall pattern of i_a. This continual reversal of axial current flow will promote the symmetrical structure seen in the system transfer function between the dendrites and the soma. This may have implications for our understanding of the process of synaptic integration. The continual reversal of axial current flow may modify the time it take for synaptic events to reach the soma and trigger an action potential. Coincidence detection on a millisecond time scale has been proposed as an mechanism underlying synaptic integration (Abeles, 1982; Softky 1995). Any mechanism, such as those reported here, which can help to shape the timing of synaptic may alter the sensitivity of the cell to coincident inputs.

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