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Dendritic Spikes Revisited

In the dendritic spikes controversy, a number of separate issues have been raised by Llinás *et al.* (*1*) in their original paper, by the subsequent comments of Hellerstein and me (*2*), and now by Zucker (*3*). Because extracellular waveshape reconstruction has been markedly clarified by the recent work of Rall and Shepherd (*4*), it has been of particular interest to see their model applied to the original data (*1*) by Zucker (*3*).

1) Do dendritic spikes exist? Undoubtedly somewhere. It is essential, however, that commonplace passive spread not be mistaken for dendritic spikes. The issue is more likely to be settled by improved experimental design than by free-parameter theoretical models, perhaps similar to the way in which the A spike was identified as coming from the initial segment region (*5*).

2) Does the Llinás *et al.* (*1*) data represent dendritic spikes or an interaction of passive sources and sinks? Because Llinás *et al.* in their original paper (*1*) did not appear to consider passive explanations despite similar prior controversies and because they interpreted "conduction velocities" quite literally, we pointed out (*2*) that a simple alternative theory (the cable model) could also easily yield conduction velocities in the same numerical range as the Llinás *et al.* data. Rall and Shepherd (*4*) have now contributed additional information which indicates that extracellularly measured conduction velocities can be quite ambiguous even when the intracellular conduction velocity is known.

3) Is cable theory or volume-conductor theory appropriate for such recordings? Cable theory is more applicable to these recordings than volume-conductor theory, and Zucker (*3*) has provided a very useful basis for deciding which theory to use for a given set of data. The fate of the extracellular currents is the underpinning of the various waveshape interpretation models. Because the physical simplicity of the cable theory assumptions utilized by ourselves, Rall and Shepherd, and Zucker are not generally appreciated, Hellerstein has prepared an additional clarification (*6*) with which I am in complete agreement.

4) Was the cable model which we utilized (*2*) adequate for our purposes? Because we were not trying to "prove" postsynaptic potential (PSP) and "disprove" dendritic spikes but merely to show that the commonplace explanation for conduction velocities was as good as the more esoteric, we chose the simplest possible model consistent with our objectives. Whereas we assumed a truly indifferent second electrode, Rall and Shepherd (*7*) more realistically assume that it records some waveform which is then subtracted from the various voltages seen by the penetrating electrode. The location of this second electrode gives rise to additional "free" parameters in the model. Because this waveform may be polyphasic, it may indeed play havoc with latency, polarity, zero-crossings, and waveshape of the differential recordings called "extracellular recordings." It is this complex effect which Zucker (*3*) utilizes to reanalyze the Llinás *et al.* data (*1*). His analysis is divided into two relatively independent sections: analysis of the "early fast transient" which has previously been the object of concern, and analysis of an underlying "slow transient." The assumptions underlying each analysis differ considerably, and his final conclusion is not directly based upon much of his preceding analyses.

5) Is Zucker's use of Rall and Shepherd's cable-plus-voltage-divider model valid for the presumably passive slow transient? Probably. By modifying their parameters, Zucker does establish the model as clearly better than classical volume-conductor models for those particular data. This Rall and Shepherd model for passive dendrites also appears to fit the data better than our similar model which lacks the subtracted waveform. In the Rall and Shepherd model for the spherical olfactory bulb, however, surface-parallel currents were unlikely to contribute to the voltage-divider current; the voltage difference between the top and bottom of the current-generating layers of the tissue (radial currents) determined the current flow through the voltage divider. In cerebellar cortex, surface-parallel currents cancel only within the volume of active cells, but currents from middle lamina may also leak out into the voltage divider. Thus the waveshape at the distant electrode may not be identical to the potential difference between the top and bottom of the active cell mass, as was the case in the Rall and Shepherd model. Nevertheless, Zucker's analysis of the slow transient is a reasonable one and clearly more inclusive than our simple model. It should be noted that at least three "free parameters" were manipulated to achieve the fit: space constant, time constant, and voltage divider setting. Furthermore, such analyses assume that the underlying process is not composite, for example, not a sequence of excitatory and inhibitory PSP's (*8*), which can be difficult to distinguish from a spike-after-hyperpolarization sequence.

6) Is Zuckers' analysis valid for the "early fast transient"? His reasoning about this key phenomena is, unfortunately, not directly based upon either his volume conductor comparisons or upon his preceding slow transient analysis. Rather, Zucker merely replots a figure from Rall and Shepherd's original calculations for mitral cells with active dendrites (using their voltage divider setting, not his) and then remarks upon the similarity to the Llinás *et al.* data, saying that this similarity rather unequivocably identifies the fast transient as a spike. The similarity does indeed suggest the possibility of dendritic spikes. To effect a serious comparison between the Rall and Shepherd model and the early fast transient data, one should at least use the new voltage divider setting and should preferably superimpose the slow transient upon the active dendrite model, since it is assumed that these dendritic spikes are set up by preceding PSP's. While the casual similarity between the figures is intriguing, it hardly justifies Zucker's firm conclusion (*3*) that this "identifies the fast transient rather unequivocably as an active spike. . . ."

7) If dendritic spikes do exist, do they propagate actively or passively down the dendrite? We raised this issue earlier because, even if all-or-nothing properties should be independently established, spikes could spread passively down the dendrites, giving rise to an apparent conduction velocity in the same manner as does a PSP. The functional implications which have been attributed to dendritic spikes assume that the dendritic spike propagates ac-

tively through the cell body and down the axon. If many different sites can thus control the neurons' output (the axon spike), Llinás *et al.* (*9*) envisage "Purkinje cells . . . as highly complex units able to attain a vast number of dynamic states which would lead to the generation of a large variety of functional patterns." Alternatively, of course, the dendritic spike might merely act more as a booster station, giving rise in the soma to something perhaps no larger than an excitatory postsynaptic potential, which would then sum together with the regular synaptic currents to determine the axon spike in the usual manner.

8) Can one "unequivocably identify" dendritic spikes by theoretical interpretation involving free parameters? Free parameter models are very useful for improving upon intuition and suggesting possibilities but are often very hazardous otherwise. Such parameters are freely adjusted for good fit by the theoretician, or they are measured from the very data that the theory attempts to predict. Their predictive usefulness is quite different from models where each parameter is independently measured and the model's prediction then compared with reality (*10*).

In summary, the present waveshape and conduction velocity interpretative techniques would seem sufficiently flexible that an unwarranted population explosion in dendritic spikes would probably take place if they were uncritically adopted. Suggestive evidence, such as the similarity to the Rall and Shepherd figures, does play an important role in the more intuitive processes by which scientific ideas are formulated, but it should not be confused with unequivocable demonstrations. Certainly, whatever the fate of dendritic spikes in Purkinje cells, Zucker's comparisons of cable theories to volume-conductor theory should prove quite helpful in the future to the neurophysiologist attempting to choose the appropriate approach to his data.

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Cable Theory and Gross Potential Analysis

There appears to be some confusion about the nature and applicability of the models used by Llinás *et al.* (*1*), Zucker (*2*), and Calvin and myself (*3*) for gross extracellular potential analysis. Calvin reviews Zucker's analysis in an accompanying note, with which I am in complete agreement. It seems that a few words of clarification are in order concerning the interpretation of gross cortical potentials.

In a population of parallel dendrites synchronously activated, extracellular currents are parallel and axial. This depends upon the packing density of the dendrites, and in neural tissue this density is high enough to assure such an axial distribution (*4*). When current flow in a resistive medium is parallel, the medium may be modeled by a resistor lying parallel to the current lines. Current flow in the interior of a dendrite may also be modeled by a resistor, because it too is axial (*5*). Hence interior and exterior media are accurately represented by two parallel resistors; the membrane of the dendrite, which couples the two media, may be represented by resistors and capacitors lying perpendicular to the dendritic axis, which connect the internal and external resistors to each other. This, then, is the cable model upon which we have drawn our conclusions regarding the interpretation of Llinás' data, and upon which Zucker has developed his critique.

A striking characteristic of the model is its symmetry about the dendritic membrane. If no values are attached to the axial resistors, it is impossible to tell the interior from the exterior of the model. This has important implications for the waveshape of the interior and exterior potentials. Because current lines are closed, any current injected into the exterior medium by a membrane "source" must be taken from the interior medium at the same point along the membrane; internally, the source appears to be a sink.

In general, from the symmetry of the model, any current source in the external medium must appear as a sink of equal strength at the same membrane locus in the internal medium, and it follows that current in the external and internal resistors must be of equal strength and of opposite sign at every point along the dendritic axis. Because potential is the integral of this current, it would appear that the internal and external potential must have the same waveshape (although different signs and amplitudes owing to different directions of current flow and different values of the axial resistances in the internal and external media).

This identity needs qualification, however. Every potential must be measured between two points. For internal and external potentials to have the same waveshape, one must use an internal reference at an "indifferent" point within the cell, that is, at a point where the membrane is at its resting potential (*6*). Similarly, for external measurements one must choose as a reference point a truly indifferent location, such as a point infinitely distant from the cell population. Under these conditions the internal and external potential indeed have the same waveshape. Because the membrane potential is the difference between the intra- and extracellular potentials, and because the difference between two potentials with the same waveshape also has that waveshape, the membrane potential has the same waveshape as the intra- and extracellular potentials. But the membrane potential is described by the cable equation, hence the cable equation describes the extracellular potential surrounding a population of synchronous parallel dendritic processes, provided that sources and sinks are introduced as driving terms to account for synaptic activity and other active membrane events.

These are the basic theoretical considerations on which our conclusions regarding Purkinje cell dendrites were based. They are founded upon the as-