

Journal Club

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One Dendritic Arbor, Two Modes of Integration

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Review of Gasparini and Magee (<http://www.jneurosci.org/cgi/content/full/26/7/2088>)

Introduction

Neurons are generally thought to be the fundamental units of computation in the brain, but recent studies in dendrites suggest that these subneuronal structures are capable of performing local computation. Although it is well established that dendrites possess a myriad of heterogeneously distributed voltage- and ligand-gated channels, how these conductances influence dendritic input integration remains unclear. On one hand, there is evidence that these channels compensate for passive cable degradation to ensure that synaptic inputs are faithfully and linearly propagated to the soma (Cash and Yuste, 1999). More recently, however, the discovery of supralinear summation and spikes in dendrites has suggested that dendrites may be capable of local nonlinear integration and computation (Polysky et al., 2004). These two views have been assumed to be contradictory. In their recent *Journal of Neuroscience* paper, however, Gasparini and Magee (2006) attempt to reconcile these two views by demonstrating that, depending on the circumstances, both forms of integration can occur. The authors then relate these two dendritic integration “states” or “modes” to simulated *in vivo* behavior.

Temporally and spatially distributed stimuli were delivered to CA1 neurons in slice using dendritic patch pipette and

two-photon glutamate uncaging. Inputs summed supralinearly and produced dendritically initiated action potentials when stimuli arrived within a short time window and clustered closely in space. In contrast, when stimuli arrived over long time windows and/or were distributed distantly in space, input summation was largely linear, and action potentials were somatically generated [Gasparini and Magee (2006), their Figs. 1 (<http://www.jneurosci.org/cgi/content/full/26/7/2088/F1>) and 2 (<http://www.jneurosci.org/cgi/content/full/26/7/2088/F2>)]. The two integration modes have distinct input–output characteristics: the supralinear summation mode requires fewer inputs to generate spikes and produces a single, precisely timed spike if the number of inputs exceeds threshold, whereas the linear summation mode requires more inputs, has more variability in spike generation, and produces multiple spikes proportional to the amount of input [Gasparini and Magee (2006), their Figs. 3 (<http://www.jneurosci.org/cgi/content/full/26/7/2088/F3>) and 4 (<http://www.jneurosci.org/cgi/content/full/26/7/2088/F4>), summarized in Table 1].

To relate these cellular integration modes to behavioral states, the authors measured the response to dendritic input that mimicked hippocampal theta and sharp wave states. Proximal inhibitory input was simulated by somatically applying a hyperpolarizing sine wave. Theta-like inputs, approximated by delivering asynchronous inputs through a dendritic pipette, produced theta-like output firing bursts [Gasparini and Magee (2006), their

Fig. 5 (<http://www.jneurosci.org/cgi/content/full/26/7/2088/F5>)]. These bursts of action potentials were mediated somatically, and their number was dependent on the number of inputs, thus obeying the rules of linear mode summation. Integration in this mode is somatocentric: the dendritic arbor behaves as an antenna propagating inputs to the soma, which then decides the action potential firing pattern.

In contrast, sharp wave-like, synchronized input summed in the nonlinear mode. The authors argue that quick and reliable neuronal responsiveness to sharp wave input is explained by the characteristics of the nonlinear mode of integration [Gasparini and Magee (2006), their Fig. 6 (<http://www.jneurosci.org/cgi/content/full/26/7/2088/F6>)]. They also demonstrate that this mode enables the dendritic arbor to generate action potentials based on specific patterns of input, that is, only those inputs that are coincident in both time and space [Gasparini and Magee (2006), their Fig. 7 (<http://www.jneurosci.org/cgi/content/full/26/7/2088/F7>)]. The nonlinear mode of summation is dendrocentric: here, the dendritic arbor behaves as a pattern detector, locally triggering an action potential if a set of inputs coincide in a specific spatial and temporal profile.

These interesting results raise several questions. First, does dendritic morphology influence summation? The authors discuss the importance of the spatial distribution of inputs but differentiate the inputs only as clustered or distributed. In these experiments, clustered inputs were triggered on a single dendritic segment,

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whereas distributed inputs were triggered on dendrites of differing diameters and spanning branch points [Gasparini and Magee (2006), their Figs. 2 (<http://www.jneurosci.org/cgi/content/full/26/7/2088/F2>) and 7 (<http://www.jneurosci.org/cgi/content/full/26/7/2088/F7>)]. This implies that supralinear integration occurs regardless of dendritic morphology, as long as the inputs are clustered closely. However, passive cable attenuation and impedance mismatch at branch points suggest that the maximum local depolarization produced by several distributed inputs will be less than the same number of clustered inputs on a single, unbroken dendritic segment, even if the resulting somatic depolarization is the same. Marked attenuation of supralinear summation across branch points has been demonstrated previously (Polsky et al., 2004). Thus, the spatial relationship between inputs and dendritic morphology may significantly influence the nature of integration.

Also, what is the role of different mechanisms of dendritic nonlinearity? The authors report that TTX-induced blockade of voltage-gated sodium channels prevents supralinear integration. Yet previously published reports attributed supralinear behavior in dendrites to NMDA and voltage-gated calcium channels (Waters et al., 2003; Polsky et al., 2004). These differences may be attributable to varying dendritic diameter, location of the dendrite on the arbor, or even variability between cell types. This discrepancy, however, suggests that further

Table 1. Integrative properties associated with each behavioral state

Behavioral state	Theta	Sharp-wave
Integration mode	Linear	Nonlinear
Integrating locus	Soma	Dendrite
Input arrival timing	Asynchronous (100–200 ms)	Synchronous (<20 ms)
Spatial distribution of inputs	Distributed	Clustered
Action potentials generated	Multiple	Single
Dendritic function	Antenna	Pattern detector

assessment of dendritic regions may be necessary to characterize integration.

Finally, how might errors in integration contribute to pathological conditions? These data suggest that the space and time window delineating nonlinear and linear forms of integration may be very small [Gasparini and Magee (2006), their Figs. 1 (<http://www.jneurosci.org/cgi/content/full/26/7/2088/F1>) and 2 (<http://www.jneurosci.org/cgi/content/full/26/7/2088/F2>)]. A sharp border between integration modes suggests that small perturbations in the ion channel milieu may cause inputs to be integrated in the wrong mode: a plausible mechanism for disease. Potassium and H-type channels have been shown to play a role in regulating integration and in epileptogenesis and would be natural candidates of interest (Hoffman et al., 1997; Shah et al., 2004).

The idea that the dendritic arbor switches between different modes of integration is a critical insight. Previous studies have presumed that dendritic integration is a monolithic process and have sought to demonstrate that integration is either primarily linear or nonlinear. Gasparini and Magee (2006) combine two

sophisticated techniques, dendritic patching and two-photon glutamate photolysis, to show that both types of integration occur and are biologically relevant. Additional work will be necessary to define the spatial and temporal rules governing each mode of integration, the possible resultant pathologies from erroneous switching, and the computational consequences of a dual-natured dendritic arbor.

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