

Integrating over time with dendritic wave-fronts

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Temporal integration, in which transient inputs shift neurons between stable firing rates, is thought to require neural networks. A new modeling study now proposes that single neurons could perform this calculation via intracellular calcium release dynamics.

How can some neural circuits hold information over a time scale of many seconds, when their biophysical building blocks cannot? In

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this issue, Loewenstein and Sompolinsky¹ address this question by proposing a model of neural integration over time that is based on a new kind of dendritic computation. Their model is mathematically appealing, although its biological plausibility remains to be determined.

A hallmark of temporal integration is multi-level persistent neural activity: neurons shifting rapidly from one stable firing rate to another in response to transient inputs. If the

change in firing rate is proportional to the input, this operation is equivalent to integration over time². Depending on the system, firing rate may be correlated with a behavioral output such as eye position³ or a variable being held in working memory⁴. Such neural systems can integrate inputs that are both positive and negative, leading to increases and decreases in firing rates, respectively.

What are the mechanisms that convert brief inputs into changes that last for many

Figure 1 A dendritic cable with tuned bistability at every point can support a wave-front moving with velocity proportional to the synaptic input. The position of the wave-front gives the time integral of the inputs.

seconds? Synaptic feedback may be important in some neural integrators; for instance, in the oculomotor system, manipulations that disrupt parts of the horizontal integrator (or communication between parts of it) reduce the persistence times of eye position⁵ and the remaining neurons (Aksay, E. *et al. Soc. Neurosci. Abstr.* 27, 852.8, 2001). This is consistent with the idea that persistent neural activity is at least partly dependent on network interactions.

However, if one assumes that neurons simply add up fast excitatory and inhibitory inputs, making a recurrent neural circuit multistable poses a significant practical challenge, as multistability requires precise tuning of synaptic feedback^{2,6}. Visual feedback can slowly tune the stability of persistent firing (Major, G. *et al. Soc. Neurosci. Abstr.* 26, 73.14, 2000). Nonetheless, brains must also operate well under a variety of conditions, including damage to the system, developmental changes and (at least in cold-blooded animals) rapid variations in temperature. Thus, even with slow tuning, the robust performance of real biological neural integrators may not be fully accounted for by recurrent feedback models.

A further place to look for mechanisms contributing to neural integration is at the level of single neurons. How would this help? One way is to imagine that a neuron is not a single point but instead is made up of many autonomous compartments. Furthermore, suppose that each compartment can have two stable voltage states: depolarized and hyperpolarized (Up and Down, respectively, in Fig. 1a). Coupling multiple bistable compartments together allows the state of one compartment to influence the states of the others, which can give rise to multiple stable states in the neuron as a whole. Neural integration could be accomplished by using many different bistable compartments.

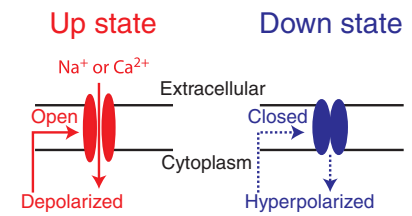
In this issue, Loewenstein and Sompolinsky¹ have implemented a version of this idea based on calcium rather than voltage bistability, by making use of an intracellular chemical signaling pathway—calcium release from internal stores. Their model is composed of four key parts. First, in each short segment of dendrite, calcium-induced calcium release (CICR) and calcium clearance are tuned to generate local bistability of intracellular calcium concentration. Each segment has stable states of low and high calcium (Fig. 1b), with shifts between states if the calcium concentration is pushed

across some threshold. Second, calcium can diffuse along the dendrite from one compartment to the next. Under certain balanced conditions, a model dendrite can be made to divide into high-calcium and low-calcium zones (Fig. 1c). With careful tuning, the boundary between the zones is stationary. Third, synaptic inputs are converted to changes in calcium concentration. The wave-front moves in one direction if the input is excitatory, and in the other direction if it is inhibitory (Fig. 1c, arrows). Fourth, the readout mechanism is current generated by a calcium-activated channel such as nonspecific cationic depolarizing conductance. This current drives the firing rate.

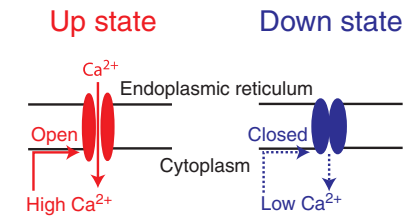
A key feature of the model is the idea that calcium release, a ubiquitous phenomenon in eukaryotic cells, including neurons, is self-amplifying⁷. Elevating cytoplasmic calcium increases the open probability of IP₃ or ryanodine receptor release channels, enabling calcium release to enhance further release. In the case of ryanodine receptors, calcium alone is sufficient to activate the channel. In the model (Fig. 1b), at low calcium levels, little calcium release is active and the concentration is set by mechanisms of calcium extrusion and reuptake. At high levels of calcium, conditions exist under which the level of calcium release is exactly sufficient to counteract extrusion/reuptake, allowing calcium to be 'latched' at a high level.

The beauty of the wave-front model is that it achieves analog temporal integration by using a single extended dendritic cable with local bistability at every point, and it does this without synaptic feedback. Like synaptic feedback-based attempts at modeling temporal integration (see discussion in ref. 8), this model still requires fine tuning of global parameters, in this case calcium release, clearance and readout. This sensitivity to parameters is unsurprising given that the core mechanism is positive feedback. Readout errors may become a particular problem in dendrites of realistic lengths³ (~1000 μm as opposed to ~30 μm in the model). The model can be made more robust with larger compartments, but at the price of losing precise temporal integration. Some help comes from the fact that the wave-front model can be elaborated to include multiple and branching dendrites, the outputs of which can be combined. This confers at least some degree of robustness to local parameter variations and random noise.

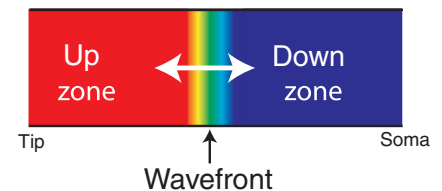
a Local voltage bistability



b Local calcium bistability



c Dendritic cable



A more serious problem in the model is the absence of an explicit mechanism for converting synaptic input to changes in calcium concentration. Even if a kick of calcium did drive a dendritic compartment into a high-calcium state, how could inhibition drive calcium down again? Speculatively, we suggest that there could be background steady-state calcium entry through voltage-gated channels, balanced by calcium pumping. An excitatory input could open more channels, causing an increase in calcium. An inhibitory input could close calcium channels, causing a dip in calcium.

Another omission is the failure to consider two known features of calcium release: gating by second messengers such as IP₃ and channel inactivation. Calcium release often requires IP₃, which is produced by extracellular activation of neurotransmitter or neuromodulator receptors. This provides a means for synaptic activity to trigger calcium release. But release duration is also limited by IP₃ degradation and diffusion, suggesting that a brief input would elevate calcium for less than a second⁹. Therefore, IP₃-based calcium release is unlikely to evoke a persistent increase in calcium concentration. Nevertheless, it might be

very well suited to be a trigger mechanism for upward transitions.

This leaves as a candidate mechanism true CICR via ryanodine receptors. But ryanodine receptors (and for that matter IP₃ receptors) usually show at least some calcium-dependent inactivation (and adaptation). These phenomena would lead to problems such as unwanted drifts in the wave-front between inputs, integration errors, and even termination of the signal. Indeed, to our knowledge, CICR-based waves are experimentally observed to propagate¹⁰ and are not 'balanced' to give a non-moving front. However, ryanodine receptor inactivation is heterogeneous; the (rare) RyR3 subtype is steeply calcium-activated and is only weakly inactivating¹¹, providing a possible substrate for the model.

Some of the problems outlined above can be circumvented by returning to voltage-based mechanisms. At the mathematical level there is no difference between the cable equation (which describes the spread of charge) and the reaction-diffusion equation (which describes the spread of ions and molecules). Furthermore, there is no real mathematical difference between voltage⁶ and calcium bistability (Fig. 1a,b). The idea that spatial activation patterns in bistable dendrites could contribute a single-cell mechanism to multistable persistent neural activity is also being explored in other integrator models¹². A natural extension would be to implement the wave-front model by

combining local voltage bistability and the cable equation.

Mechanisms based on voltage multistability have several advantages. The voltage-dependent conductances underlying such a scheme could include persistent sodium, long-lasting calcium and NMDA conductances, all of which have an established track record of involvement in bistability and indeed multistability in many different neuron types¹³. In particular, NMDA conductance is abundant in candidate integrator neurons (Wang, S.S.-H. *et al. Soc. Neurosci. Abstr.* **24**, 602.5, 1998) and is necessary for normal integration *in vivo*¹⁴. Because these conductances are voltage-gated, inputs could drive both upward and downward transitions. A voltage-based mechanism also removes the need for a calcium-to-firing conversion step. One weakness is that the dendritic cable would be much more compact electrically than for calcium diffusion, but if membrane conductance is sufficiently high, as may occur *in vivo*, dendrites may be sufficiently 'long' in electrical terms to support plateau potential wave-fronts. Cable nonuniformities or heterogeneity¹² may be required for correct readout. Another weakness of the voltage wave-front idea is that it does not explain why transient intracellular current injections in integrator neurons do not evoke persistent changes in firing^{1,15}. However, this discrepancy can also be explained if current injections affect additional conductances that mask changes in dendritic state¹⁵. In short, a voltage-based proposal would be mathemati-

cally similar to the existing calcium-based model, and may be more plausible biologically.

Models that have aimed to explain how neural circuits generate persistent activity have suggested various underlying mechanisms, including tuned recurrent feedback, cellular or dendritic bistability, and now calcium release wave-fronts. Neural circuits may even use some combination of these to improve robustness¹². The definitive tests, however, will be experimental. To paraphrase the embryologist Viktor Hamburger, "Our real teacher is the nervous system, who is, incidentally, the only teacher who is always right."

1. Loewenstein, Y. & Sompolinsky, H. *Nat. Neurosci.* **6**, 961–967 (2003).
2. Robinson, D.A. *Annu. Rev. Neurosci.* **12**, 33–45 (1989).
3. Aksay, E., Baker, R., Seung, H.S. & Tank, D.W. *J. Neurophysiol.* **84**, 1035–1049 (2000).
4. Goldman-Rakic, P.S. *Neuron* **14**, 477–485 (1995).
5. Arnold, D.B. & Robinson, D.A. *Exp. Brain Res.* **113**, 57–74 (1997).
6. Koulikov, A.A., Raghavachari, S., Kepecs, A. & Lisman, J.E. *Nat. Neurosci.* **5**, 775–782 (2002).
7. Berridge, M.J., Lipp, P. & Bootman, M.D. *Nat. Rev. Mol. Cell Biol.* **1**, 11–21 (2000).
8. Seung, H.S., Lee, D.D., Reis, B.Y. & Tank, D.W. *J. Comp. Neurosci.* **9**, 171–185 (2000).
9. Khodakhah, K. & Ogden, D. *J. Physiol.* **487**, 343–358 (1995).
10. Jaffe, L.F. *BioEssays* **21**, 657–667 (1999).
11. Fill, M. & Copello, J.A. *Physiol. Rev.* **82**, 893–922 (2002).
12. Goldman, M.S., Levine, J.H., Major, G., Tank, D.W. & Seung, H.S. *Cereb. Cortex* (in press).
13. Simon, M., Perrier, J.F. & Hounsgaard, J. *Eur. J. Neurosci.* **18**, 258–266 (2003).
14. Mettens, P., Cheron, G. & Godaux, E. *Neuroreport* **5**, 1333–1336 (1994).
15. Aksay, E., Gamkrelidze, G., Seung, H.S., Baker, R. & Tank, D.W. *Nat. Neurosci.* **4**, 184–193 (2001).