EPPENDORF WINNER

The Language of Dendrites

Dendrites perform spatial and temporal discrimination during input processing.

Tiago Branco

> Theoretical neurophysiology rests on certain cardinal assumptions. … Their adjunctions, or synapses, are always between the axon of one neuron and the soma of another.
>
> McCulloch and Pitts, 1943

Animal survival depends on the ability to analyze the environment and act on it: escape predators, find food, select a mate. Understanding how the brain achieves this is one of the most fascinating and challenging problems in neuroscience. What sequence of steps converts sensory cues into behavior? In other words, how does the brain compute? In 1943, McCulloch and Pitts noted that neurons firing action potentials act like binary devices that can either be on or off. In a seminal paper (*1*), they showed how connected networks of neurons could represent any logical expression, and 60 years of subsequent work in theoretical neuroscience has devised models of neuronal networks that can implement computational tasks. The basic operation in these models is the conversion of input into action potentials—the process of turning a neuron on. How is this conversion achieved? What are the rules for integrating input, and what kind of information can a single neuron interpret and process? The traditional view is that neurons sum input and, if the sum reaches a certain threshold, an action potential is triggered. The important variable is thus the amount of synaptic input—if neurons had a language and each synapse were a letter, they would only care about how long a word is. However, most neurons seem to have the ability to be more powerful than this. Contrary to the assumption of McCulloch and Pitts, synapses are not made onto the soma (cell body) but onto dendrites, protrusions from the cell body separating the input and the action potential initiation zone. Dendrites filter, transform, and compute thresholds of synaptic input and can, in theory, implement basic arithmetic operations by themselves (*2*). I first became interested in dendrites during my Ph.D. work. Monitoring the properties of single synapses in hippocampal neurons, I found that dendrites can implement a negative feedback that regulates the amount of input each branch receives (*3*). Dendrites can thus independently process and regulate input information. Can these properties be used by single neurons to perform high-order computations?

One of the most important features of animals and the surrounding environment is the dynamic nature of their interaction. Input to neurons arrives in temporal sequences, which depend on where the animal is and what it is doing. Can neurons distinguish between different sequences of synaptic input? Can they tell the difference between "danger" and "garden," or are they both the same six-letter-long word? This was the first question I asked in my postdoctoral research, together with my collaborators at University College London. We

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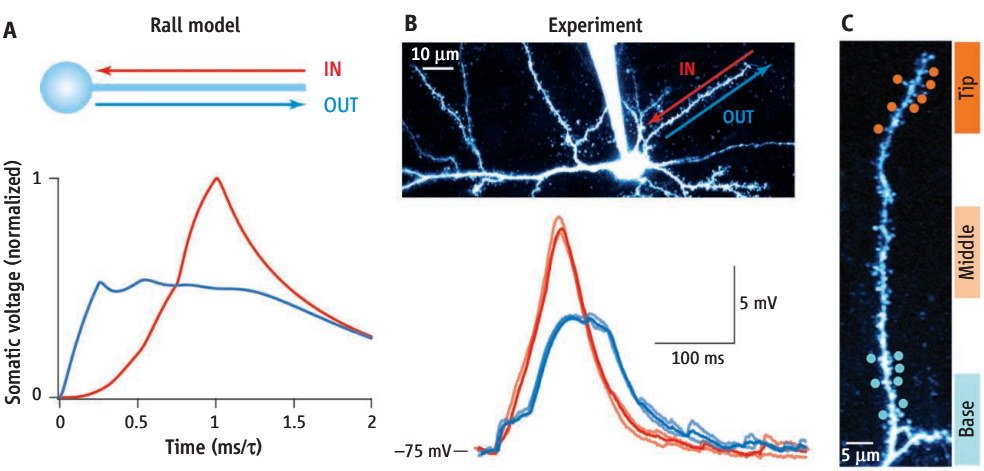
eppendorf & Science PRIZE FOR NEUROBIOLOGY

Eppendorf and *Science* are pleased to present the prize-winning essay by Tiago Branco, the 2011 winner of the Eppendorf and *Science* Prize for Neurobiology.



Dendritic computation in pyramidal cells. (**A**) The original Wilfrid Rall model, where somatic potentials are larger in the IN activation sequence because of cable filtering (τ , membrane time constant). (**B**) Somatic potentials recorded during activation of eight synapses along a dendrite (top, cortical pyramidal cell in layer 2/3 filled with a fluorescent dye showing the dendrite selected for the experiment). The IN sequence is larger than the OUT, but unlike the model, differences are due to differential activation of NMDA receptors. (**C**) A cluster of seven synapses was selected at different regions of a dendritic branch [orange spots, distal; blue spots, proximal; bars on the right show color-code of plots in (D)]. (**D**) The input-output function is progressively steeper toward the distal end of the branch, and somatic potentials are less sensitive to input timing (EPSP, Excitatory postsynaptic potential). [Panels (C) and (D) originally published in (*7*), reprinted with permission]

were not entirely naïve about what to expect, as Wilfrid Rall had predicted in 1964 that dendritic filtering of synaptic potentials propagating to the soma should introduce time delays to their peak and confer some degree of sequence sensitivity (*4*) (figure, panel A). However, testing this experimentally required precise spatial and temporal control of synaptic activation, which only recently became technically possible with the development of two-photon laser glutamate uncaging (*5*). Using this technique in slices of rat brain cortex, I first tested Rall's prediction: After selecting 8 to 10 synapses distributed over one dendritic branch, I activated them sequentially and in two opposite directions while measuring the voltage response at the soma with whole-cell patch clamp, as well as dendritic calcium levels with a second two-photon laser (*6*). The results showed what Rall had predicted—responses were larger in the IN than in the OUT direction (figure, panels A and B), but with an unexpected twist. If *N*-methyl-D-aspartate (NMDA) receptors were blocked, the response was the same for both directions, suggesting that the mechanism was different from passive filtering. To understand these results, I constructed several compartmental models and found that the difference between the two sequences was due to the interaction between the impedance gradient along dendritic branches and the nonlinear voltage sensitivity of the NMDA receptors. Testing thousands of different sequences in the model led to the prediction that neurons should be able to resolve more than just the IN and OUT sequences, which I then confirmed experimentally. Further modeling and experiments extended these findings and showed that the probability of discriminating any two random sequences is very high and that this applies to a variety of spatial input distributions. During these experiments, I became interested in a related problem. Dendrites introduce a spatial dimension to synaptic integration, with synapses activated all over the dendritic tree. Does synaptic location matter? Are the rules of integration the same for the entire dendritic tree? Using the same set of techniques, I measured how different regions of single dendritic branches integrated increasing numbers of activated synapses and how they responded to different degrees of input synchrony (*7*). I found that distal regions amplified synaptic input with high gain, displaying a very steep sigmoidal input-output function, and were remarkably insensitive to input timing. In contrast, moving the input toward the proximal part of the branch progressively generated more linear integration curves with small gain, which required high input synchrony for summation (figure, panels C and D). Pharmacological experiments showed that these properties rely on recruitment of voltage-gated calcium and sodium channels and crucially on NMDA receptors. Compartmental modeling showed that local differences in synaptic integration can again be explained by voltage-sensitive conductances acting on a gradient of impedance, whereby high-impedance distal regions are increasingly efficient in recruiting voltage-gated channels. Overall, the results of this research show that dendrites implement the complex computational task of discriminating temporal sequences and allow neurons to differentially process inputs depending on their location, suggesting that the same neuron can use multiple integration rules. The current challenge is to find out how neuronal circuits exploit these properties in vivo and how we should update our set of cardinal assumptions for theoretical neurophysiology. As we begin to understand the language of dendrites, we can start eavesdropping on their conversations and learn more about how the brain accomplishes its tasks.

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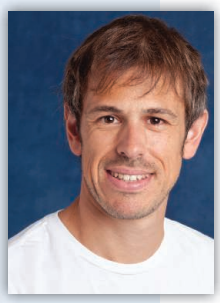
2011 Grand Prize Winner



The author of the prize-winning essay, **Tiago Branco**, received his M.D. from Lisbon University in 2002. He then joined the Wellcome Trust Four-Year Ph.D. Program in Neuroscience at University College London, where, in Yukiko Goda's group, he focused on neurotransmitter release properties of individual synapses. After receiving his Ph.D., he moved to Michael Hausser's laboratory, where he has been a postdoctoral research fellow since 2007. Dr. Branco has applied electrophysiological, optical, and modeling techniques to investigate how dendritic integration contributes to single-neuron computations. He plans to combine this approach with molecular methods to investigate the role of dendrites in controlling animal behavior.

Finalists

Aaron Gitler, for his essay "A Simple Yeast Model Provides New Insight into a Complicated Human Neurodegenerative Disease." Dr. Gitler is an assistant professor in the Department of Cell and Developmental Biology at the University of Pennsylvania School of Medicine. He received his Ph.D. from the University of Pennsylvania, working with Jonathan Epstein on signaling pathways in cardiovascular development. In postdoctoral research with Susan Lindquist, at the Whitehead Institute for Biomedical Research, he performed yeast genetic screens for modifiers of toxicity associated with the Parkinson's disease protein α-synuclein. Dr Gitler's group at the University of Pennsylvania combines yeast and human genetics to elucidate novel pathways involved in neurodegenerative disease, focusing on the motor neuron disease amyotrophic lateral sclerosis.

Roger Clem, for his essay "An Uninstall Function for Fear Memory." Dr. Clem received his Ph.D. under the mentorship of Alison Barth at Carnegie Mellon University, where he investigated sensory-driven synaptic plasticity in the neocortex. During a postdoctoral fellowship with Rick Huganir at The Johns Hopkins University, Dr. Clem examined the role of glutamate receptor trafficking in emotional memory. His work explains how fear memories can be permanently weakened through behavioral training in a process akin to software uninstall routines. Dr. Clem has accepted an appointment to assistant professor of neuroscience at the Mount Sinai School of Medicine, where he will investigate synaptic mechanisms in memory formation and updating, as well as how those processes might be manipulated to treat psychiatric conditions.

For the full text of finalist essays and for information about applying for next year's awards, see *Science* Online at www.sciencemag.org/feature/data/prizes/eppendorf/.

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