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The Quest for Action Potentials in *C. elegans* Neurons Hits a Plateau

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Ever since the publication of the anatomical wiring diagram of the *C. elegans* nervous system¹, there has been strong interest in the question of the basic operating principles of *C. elegans* neurons. Though necessary, a wiring diagram by itself is insufficient to explain behavior; one also needs to know the intrinsic electrical properties of the neurons. Do they act as passive or active nodes? If active, do they fire all-or-none action potentials, graded regenerative responses, or something else? With the introduction of specialized electrophysiological methods for patch-clamping *C. elegans* neurons^{2–5}, several laboratories are now addressing these questions directly. A recent paper by Mellem et al.⁶ reports the surprising finding that the answer, at least in some *C. elegans* neurons, is “something else.”

Recording *in situ* from the motor neuron class RMD, Mellem et al. noted a distinctive regenerative response to current injection. A brief pulse of positive current in an RMD neuron (or a puff of glutamate) elicited a depolarization of more than 30 mV that was stable for at least 1 min (Fig. 1A), but could be terminated by a brief pulse of negative current. Thus, RMD has two stable resting potentials, one near –70 mV and one near –35 mV. Importantly, shifts between the two resting potentials were also observed to occur spontaneously, indicating that these events probably happen naturally in RMD neurons.

Electrophysiologists have described four main types of regenerative events: action potentials, graded potentials, intrinsic oscillations, and plateau potentials (Fig. 1B). The defining features of action potentials are well known — they are all-or-none depolarizations with a stereotypical waveform that is invariant with respect to the amplitude and waveform of the triggering stimulus. The defining features of other types of regenerative events may be less well known. Graded potentials resemble action potentials except that their amplitude and waveform are sensitive to amplitude and waveform of the stimulus. Intrinsic oscillations, such as those that underlie endogenous bursting, are slow, cyclic alterations in membrane potential caused by antagonistic voltage-dependent currents. Plateau potentials are prolonged, all-or-none depolarizations that can be triggered and terminated by brief positive and negative current pulses, respectively⁸.

Regenerative activity has been seen before in nematode neurons. In *Ascaris*, motor neurons fire graded potentials in response to the offset of hyperpolarizing current pulses¹⁵. Inhibitory motor neurons exhibit slow oscillations that are mostly likely intrinsic¹⁶, as do certain ventral cord interneurons^{17, 18}. There is also indirect evidence of Ca²⁺-dependent action potentials in the ventral nerve cord¹⁹. In *C. elegans*, depolarizing current pulses in chemosensory neurons elicit active responses that outlast the stimulus pulse². The events recorded by Mellem et al. fit the criteria of plateau potentials perfectly in that they are long-lasting, all-or-none events that can be terminated by a negative current pulse. In addition, genetic manipulations and ion-substitution experiments performed by Mellem et al. suggest that RMD plateau potentials depend on a current carried mainly by Na⁺ and Ca²⁺ ions,

which is consistent with the biophysical mechanisms of plateau potentials in other organisms^{9–14}.

The discovery of plateau potentials in *C. elegans* neurons is an important development, for it greatly expands the computational repertoire of the *C. elegans* nervous system. Plateau potentials are the biological equivalents of Schmitt triggers which have many interesting applications including oscillators, timers, and flip-flop elements. Thus, it is not surprising that plateau potentials have been reported in a wide range of vertebrate and invertebrate organisms^{29–35}, where they have been implicated in such functions as pattern generation and short-term memory. At present, almost nothing is known about either function in *C. elegans*, despite long-standing behavioral evidence of multiple pattern generators^{36–38} and several forms of associative and nonassociative learning³⁹.

The findings of Mellem et al. raise many new questions that the field will now be keen to answer. (1) Do most *C. elegans* neurons exhibit plateau potentials? If not, which functional subsets of neurons exhibit them, and what purposes do they serve? (2) Is plateau behavior an intrinsic property of *C. elegans* neurons, or does it arise, at least in part, through synaptic interactions? The latter is a possibility because at least some *C. elegans* neurons appear to release neurotransmitter at the resting potential^{27, 28}. (3) What ion channels are required for plateau potentials, and how might they be regulated by learning and other forms of experience?

The quest for action potentials in *C. elegans* neurons is really just beginning. To date, current-clamp recordings have been published for only four of the 118 functional classes of neurons in *C. elegans*^{2, 6, 20, 21}; thus action potentials may yet be found in some classes of neurons. But if action potentials turn out to be the main currency of information transfer in *C. elegans*, it may come as something of a surprise, at least to theoreticians who have considered the signaling properties of neurons near what might be termed the small-cell limit. At this spatial scale, there may be only a few tens or hundreds of sodium and potassium channels in an entire neuron, and input resistance is so high that the opening of a single sodium channel can trigger an action potential, or what is left of one. Many *C. elegans* neurons are likely to be nearly isopotential², and reducing isopotential model neurons to the small-cell limit has profound effects on signaling. For example, when a Hodgkin-Huxley model is reduced, an otherwise silent neuron fires tonically at average rates of tens of spikes per second^{22, 23}. Moreover, firing is so irregular that the standard deviation of interspike intervals approaches the size of the intervals themselves. Together, these two effects render coding schemes based on firing rate and spike timing essentially unworkable. Additional problems arise when one considers spike propagation along thin axons (diam. < 500 nm), including spurious or deleted spikes and the redistribution of spike arrival times²⁴.

Evidence that *C. elegans* neurons operate at the small-cell limit is already quite strong. Measured input resistances in medium sized *C. elegans* neurons are on the order of G-ohms² and the true input resistance is likely to be much higher when one takes into account the G-ohm order leak of the seal resistance in a whole-cell patch clamp experiment. In this range, the opening of a single ion channel can cause voltage fluctuations on the order of millivolts to tens of millivolts. Process diameters of most *C. elegans* neurons are in the range of 100 – 200 nm²⁵, and it is estimated that chemosensory neurons, whose size and morphology are typical of most neurons in the worm's head, have only about 50 voltage dependent calcium channels², the likely carriers of inward current in *C. elegans*²⁶. Coding schemes based on the amplitude or duration of graded potentials are also probably unworkable, as these parameters too would be strongly sensitive to the random behavior of small numbers of highly effective channels. Thus, however *C. elegans* neurons may code information, it is

likely to be different from the way it is done in the nervous systems with which we are currently more familiar, which have much larger neurons.

Perhaps the greatest significance of the finding of plateau potentials in *C. elegans* neurons is the prospect of an elegant solution to the small-cell coding problem: How is information represented when both action potentials and graded potentials are unreliable? In *C. elegans*, the small cell problem is particularly acute because there are at most six neurons in any functional class, a fact that eliminates averaging across multiple neurons as a remedy. Action potentials and graded potentials support analog coding schemes — firing rate and spike timing are analog quantities — whereas plateau potentials might support a digital coding scheme in which neuronal state (depolarized or hyperpolarized) stores the sign of the most recent synaptic input. Digital codes are, of course, famous for their immunity to noise, spurious voltage offsets, and other likely afflictions of small-neuron networks. There are already tantalizing hints that the direction of locomotion in *C. elegans* (forward vs. reverse) is coded digitally⁴⁰. If it turns out that plateau potentials are the dominant mode of electrical signaling in *C. elegans*, we might soon be getting our first look at a digital nervous system.

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Fig. 1.

A. Representation of a quasi-stable plateau potential in *C. elegans* RMD neurons. A positive current pulse (lower trace) elicits a regenerative depolarizing response followed by a sustained plateau (upper trace). Thus, RMD has two resting membrane potentials (V_m). The plateau can be terminated by a negative current pulse (after Mellem et al. 2008). B. Four common types of regenerative neuronal activity. Intrinsic oscillations and plateau potentials are frequently accompanied by trains or bursts of spikes in neurons capable of firing action potentials (vertical lines). Dashed lines indicate amplitudes of all-or-none events.