Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Lessons from a Compartmental Model of a *Drosophila* Neuron

John C. Tuthill

University of Chicago, Chicago, Illinois 60637, and Howard Hughes Medical Institute Janelia Farm Graduate Program, Ashburn, Virginia 20147

Review of Gouwens and Wilson

Although the vinegar fly, *Drosophila melanogaster*, has been a biological model organism for over a century, its emergence as a model system for the study of neurophysiology is comparatively recent. The primary reason for this is that the vinegar fly and its neurons are tiny; up until 5 years ago, it was prohibitively difficult to record intracellularly from individual neurons in the intact *Drosophila* brain (Wilson et al., 2004). Today, fly electrophysiologists can genetically label neurons with GFP and reliably record from many (but not all) neurons in the fruit fly brain. Using genetic tools to drive expression of fluorescent calcium indicators, light-sensitive ion channels, or cell activity suppressors, we are beginning to understand how the external environment is represented with electrical potentials in *Drosophila* neurons (for review, see Olsen and Wilson, 2008).

Despite this impressive résumé, there is still no consummate approach for monitoring neural activity in the vinegar fly brain. In addition to many of the same methodological quandaries that plague vertebrate electrophysiologists, *Drosophila* neurons pose several additional problems. First, there is an important morphological distinction between invertebrate and vertebrate neurons. Vertebrate neurons are typically multipolar: the soma gives rise to multiple processes. In a fully developed multipolar neuron, the cell body is located centrally—its role is to sum dendritic potentials before spike initiation within the initial segment of the axon (Mainen et al., 1995). However, the majority of invertebrate neurons, such as those in vinegar flies, have a unipolar morphology. In a unipolar neuron, a single fiber originates from the cell body. This process either bifurcates into one axonal arbor and one dendritic arbor, or in some cases there is no bifurcation and multiple branches arise directly from the main axonal shaft (Strausfeld, 1976).

Due to its unipolar structure, the cell body of a *Drosophila* neuron is electrotonically segregated from other regions of the cell, and does not appear to be involved in synaptic integration. As a result, action potentials recorded at the cell body are greatly attenuated and can be difficult to distinguish from other synaptic potentials. Another consequence is that fixing the membrane potential of a *Drosophila* neuron at the soma may have little effect on the electrotonically distant axon, where spikes initiate in other invertebrates (Sandeman, 1969; Hoyle and Burrows, 1973).

A second property of *Drosophila* neurons, their small size, further constrains the methods used to study their electrical properties. A typical neuron in the head of *Drosophila melanogaster* has a soma diameter of 2–6 μm, compared with 10–30 μm for a pyramidal cell in rodent cortex (Larkman and Mason, 1990). In larger neurons, recordings can be made from either the soma or dendrites, but most recordings in diminutive *Drosophila* neurons are made by patch clamping the cell body. *Drosophila* neurons can be so small that a patch seal at the soma might significantly distort the passive properties of the cell.

A recent study in *The Journal of Neuroscience* addressed these concerns by building a compartmental model of a well studied neuron in the vinegar fly olfactory system (Gouwens and Wilson, 2009). Compartmental modeling is a technique that can be traced to the pioneering work of Wilfrid Rall, who suggested a method to extend analysis of current flow in finite cables to certain kinds of branched neurons (Rall, 1959). In a compartmental model, a neuron is divided into small segments, or compartments, each of which is described by an ordinary differential equation. The process is classically completed in three steps: (1) the morphology of the neuron is reconstructed, (2) the biophysical parameters of the neuron are estimated by injecting square pulses of current and measuring voltage changes, and (3) the resulting family of differential equations is solved. The end product is a mathematical model of how current propagates through the neuron. Though by no means precise, compartmental models have been effectively used to explain experimental data, create new testable hypotheses, and simulate the properties of neurons when electrophysiological mea-

Received July 13, 2009; revised Aug. 16, 2009; accepted Aug. 18, 2009.

Eugenia Chiappe, Vivek Jayaraman, and Michael Reiser provided helpful comments on the manuscript.

Correspondence should be addressed to John C. Tuthill, Janelia Farm Research Campus, 19700 Helix Drive, Ashburn, VA 20147. E-mail: tuthillj@janelia.hhmi.org.

DOI:10.1523/JNEUROSCI.3348-09.2009

Copyright © 2009 Society for Neuroscience 0270-6474/09/2912033-02$15.00/0

surements prove technically impractical (for review, see Herz et al., 2006).

Gouwens and Wilson (2009) used a fitting algorithm to determine the membrane parameters that best fit their electrophysiological data, and then tested their fit against the cell's response to injection of white-noise current. They used this method to estimate the passive properties of the projection neuron (PN), a second-order olfactory neuron located in the fly antennal lobe. Olfactory receptor neurons (ORNs) in the fly antennae project to olfactory glomeruli, where they form strong synapses on the PNs. Each PN receives input from a single class of ORNs, and a single spike in one ORN axon is sufficient to trigger large and reliable postsynaptic potentials in a PN (Kazama and Wilson, 2008).

After fitting the membrane parameters to the data, Gouwens and Wilson (2009) used their compartmental model to answer several questions about *Drosophila* neurons. By voltage clamping the soma of their model neuron, they found that an electrode at the PN soma does not effectively control the membrane voltage in the dendritic tuft and axonal arbor. This space-clamp problem is distressing, though not particularly surprising given that somatic voltage clamp imperfectly controls dendritic voltage in rat layer 5 pyramidal neurons (Williams and Mitchell, 2008).

The authors then attempted to locate the spike initiation zone of the PN cell by simulating spike waveforms propagating from different locations in the cell and comparing them to the filtered waveforms recorded at the soma. They found that action potentials likely initiate near the first axonal segment, similar to multipolar neurons (Mainen et al., 1995). This is not necessarily true for all *Drosophila* neurons—cells with multiple arbors could even have more than one spike initiation zone, as in the locust lobula giant motion detector neuron (O'Shea, 1975).

Gouwens and Wilson (2009) used another trick to estimate how a recording electrode alters the resting potential of a real PN cell. They first measured the spontaneous firing rate of the neuron extracellularly, in cell-attached mode. They then switched to whole-cell mode and varied the holding current so that the cell fired at a range of frequencies. The point at which the whole-cell firing rate matched the cell-attached firing rate provided an estimate of the true resting potential of the cell. It turns out that the resting potential of the PN is ~10 mV more hyperpolarized than the potential measured at the soma with a patch electrode. This is likely due to the high input resistance of *Drosophila* neurons, which allows some current to leak out around the electrode seal.

Does this mean that we will have to build a compartmental model for every cell type in the fly brain? Potentially, yes, if we hope to correctly interpret what our electrodes are measuring. Unfortunately, the technique used by Gouwens and Wilson (2009) to measure the true resting potential of the PN cell is applicable only to spiking cells. The biases introduced by whole-cell recordings may be more difficult to understand in cells that signal via small shifts in subthreshold activity. For example, recordings from lobula plate tangential cells in the optic lobe of *Drosophila* demonstrated that these cells exhibit directionally selective changes in membrane potential, in addition to small, TTX-sensitive "spikelets" (Joesch et al., 2008). Compartmental modeling could be used to correct for electrotonic filtering in these neurons, but other methods will be needed to measure current leakage around the electrode seal in nonspiking cells.

Even with a detailed compartmental model, the electrophysiological properties of a neuron cannot be definitively resolved by recording at the cell body. Voltage-and calcium-dependent channels play an important role in determining the electrophysiological properties of neurons (Marder, 1998). In the fly, antidromic propagation of action potentials from the spike initiation zone to the cell soma could be influenced by voltage-gated conductances, or somatic activity may reflect spikes originating in the dendrites which do not correspond to the axonal output of the neuron. Even if one were to identify the sodium-dependent spikes using TTX, somatic spikes in *Drosophila* neurons can be so small that they are hard to distinguish from large EPSPs (Gouwens and Wilson, 2009).

Another recent paper published in *The Journal of Neuroscience* showed that a model neuron with a particular electrophysiological phenotype could be built from many different distributions of conductances (Taylor et al., 2009). The authors demonstrated that multiple conductances underlie specific properties such as input conductance and membrane potential, and these conductances are only weakly correlated between different models with the same phenotype. This suggests that even if we did know all the conductances within a particular neuron, it would be difficult to predict how they interact to produce a neuron's electrophysiological disposition.

Despite these limitations, the compartmental model constructed by Gouwens and Wilson (2009) provides a careful example for *Drosophila* neurobiologists. Before plunging into the brain with electrodes and genetic constructs, it is crucial to understand how a measurement or manipulation affects a neuron's electrophysiological properties. With the rapid development of new methods for monitoring and controlling neural activity, significant effort is required to interrogate and validate the efficacy (or inefficacy) of each technique under a variety of experimental conditions.

References

Gouwens NW, Wilson RI (2009) Signal propagation in *Drosophila* central neurons. J Neurosci 29:6239–6249.

Herz AV, Gollisch T, Machens CK, Jaeger D (2006) Modeling single-neuron dynamics and computations: a balance of detail and abstraction. Science 314:80–85.

Hoyle G, Burrows M (1973) Neural mechanisms underlying behavior in the locust *Schistocerca gregaria.* I. Physiology of identified motorneurons in the metathoracic ganglion. J Neurobiol 4:3–41.

Joesch M, Plett J, Borst A, Reiff DF (2008) Response properties of motion-sensitive visual interneurons in the lobula plate of *Drosophila melanogaster.* Curr Biol 18:368–374.

Kazama H, Wilson RI (2008) Homeostatic matching and nonlinear amplification at identified central synapses. Neuron 58:401–413.

Larkman A, Mason A (1990) Correlations between morphology and electrophysiology of pyramidal neurons in slices of rat visual cortex. I. Establishment of cell classes. J Neurosci 10:1407–1414.

Mainen ZF, Joerges J, Huguenard JR, Sejnowski TJ (1995) A model of spike initiation in neocortical pyramidal neurons. Neuron 15: 1427–1439.

Marder E (1998) From biophysics to models of network function. Annu Rev Neurosci 21:25–45.

Olsen SR, Wilson RI (2008) Cracking neural circuits in a tiny brain: new approaches for understanding the neural circuitry of *Drosophila.* Trends Neurosci 31:512–520.

O'Shea M (1975) Two sites of axonal spike initiation in a bimodal interneuron. Brain Res 96:93–98.

Rall W (1959) Branching dendritic trees and motoneuron membrane resistivity. Exp Neurol 1:491–527.

Sandeman DC (1969) The site of synaptic activity and impulse initiation in an identified motoneurone in the crab brain. J Exp Biol 50:771–784.

Strausfeld NJ (1976) Atlas of an insect brain. Berlin: Springer.

Taylor AL, Goaillard JM, Marder E (2009) How multiple conductances determine electrophysiological properties in a multicompartment model. J Neurosci 29:5573–5586.

Williams SR, Mitchell SJ (2008) Direct measurement of somatic voltage clamp errors in central neurons. Nat Neurosci 11:790–798.

Wilson RI, Turner GC, Laurent G (2004) Transformation of olfactory representations in the *Drosophila* antennal lobe. Science 303: 366–370.