Mechanisms by Which Cell Geometry Controls Repetitive Impulse Firing in Retinal Ganglion Cells

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Fohlmeister, J. F. and R. F. Miller. Mechanisms by which cell geometry controls repetitive impulse firing in retinal ganglion cells. J. Neurophysiol. 78: 1948–1964, 1997. Models for generating repetitive impulse activity were developed based on multi-compartmental representations of ganglion cell morphology in the amphibian retina. Each model includes five nonlinear ion channels and one linear (leakage) channel. Compartmental distribution of ion channel type and density was designed to simulate whole cell recording experiments carried out in the intact retina-eye cup preparation. Correspondence between the model and physiology emphasized channel-specific details in the impulse waveform, based on phase plot analysis, frequency versus current (F/I) properties, and interspike trajectories for current injected into the soma, as well as the ability to conduct impulses in both orthodromic and antidromic directions. Two general types of model are developed, including equivalent cylinder representations and more realistic compartmentalizations of dendritic morphology. These multicompartmental models include representations for dendritic trees, soma, axon hillock, a thin axonal segment, and axon distal to thin segment. A large number of compartments (~800) representing a single neuron were employed to ensure that maximum voltage differences between neighboring compartments during the steepest rates of change of membrane potential were acceptable small. Leakage conductance varied from 3 to 8 μS/cm². The results establish that intercompartmental currents, due to inhomogeneous morphology, dominate membrane currents in the interspike intervals and thus play a major role in determining the impulse spacing and the information carried by impulse trains. Variations in input resistance are far less important than the degree to which ion channels are present in the dendritic compartments for the regulation of F/I properties. Cell geometry, including the thin axonal segment, places significant constraints on the location of ion channels required to support impulse initiation and propagation in both the ortho- and antidromic directions. The site of impulse initiation varies greatly and depends on the stimulus magnitude. Models that conform to physiological constraints also show irregular firing, particularly for near threshold stimulation of the soma, due to multiple sites of impulse initiation. Such behavior could represent an asset to the cells for conveying information under conditions of low contrast stimulation. Multiple spike initiation zones also can provide retinal ganglion cells with a variety of response characteristics, including spike doublets, depending on the level of cell activation. Increasing the diameter of the dendritic equivalent cylinder reduces the impulse frequency (F/I) response. Over a restricted range of ion channel densities in the dendritic tree, phase locking between dendritic membrane oscillations and somatic spiking can occur with dendritic stimulation, and mathematical chaos can be demonstrated when sufficiently thin dendritic processes are present. We conclude that cell morphology is the primary factor in determining firing patterns and the impulse frequency response of a given cell and that differences in channel density distribution across a population of cells plays, at most, a secondary role in this function. This conclusion applies to both synaptic activation and electrode stimulation of the soma.

INTRODUCTION

When synaptically mediated information traverses through the vertebrate retina, its final effect is to alter the excitability of retinal ganglion cells. Ganglion cells are organized to convert the analogue signal processing carried out by presynaptic neurons to the all-or-none encoding and propagation of impulse activity. It is assumed widely that the impulse-generating mechanism resides primarily in the axon hillock (Carras et al. 1992; Coombs et al. 1957) and thus reflects the collective pooling of synaptic currents applied to the dendrites and soma. A recurring question—related to the impulse activity—concerns the role that the dendrites and soma play in controlling or participating in impulse generation.

Most ganglion cells appear to support sustained impulse activity to constant current injection irrespective of the transient or sustained nature of their light-evoked discharge pattern. This suggests that transient versus sustained firing patterns are determined by the retinal network and synaptic currents rather than being intrinsic properties of individual ganglion cells. Until recently, no model of repetitive impulse activity was available that permitted exploration of the role that different anatomic partitions of these neurons might play in the generation and support of repetitive impulse activity. However, in the last several years, a number of laboratories generated detailed information on the types and magnitudes of ionic currents that are generated by ganglion cells in response to voltage displacements of the cell membrane. Data of this type are now available for amphibians (Lukasiewicz and Werblin 1988), turtles (Lasater and Witkovsky 1990), fish (Kaneda and Kaneko 1991), and mammals (Lipton and Tauck 1987). Based on these experimental results, gating kinetics were developed for five nonlinear ion channels that reproduced the essential features of impulse activity, including the impulse waveform and sustained firing pattern evoked by depolarizing stimulus current (Fohlmeister et al. 1990). These kinetics were explored in a more detailed single compartment model in the companion paper (Fohlmeister and Miller 1997).

The present study extends the analysis of single-compartment models to include more realistic, multicompartmental representations of retinal ganglion cell morphology and evaluates the role that different anatomic partitions of the cell might play in supporting impulse generation and propaga-
tion. We included in the models representations of dendritic trees, soma, axon hillock, and the axon, including the narrow axonal segment described in anatomic studies (Carras et al. 1992; Stell and Witkovsky 1973). In addition, the distribution of Na, K, and Ca channels was manipulated throughout the neuron to evaluate possible roles that a heterogeneous ion channel distribution might play in impulse encoding. These studies were constrained by physiological recordings, obtained with whole cell electrodes from ganglion cells in the intact, superfused retina-eyecup preparation of the mudpuppy and tiger salamander retinas. The results of this study establish new insights into the functional partition of retinal ganglion cells for the initiation and support of repetitive impulse activity. Both the dendrites and thin segment (or narrow region) of the axon appear to play important roles in initiating and controlling impulse activity. The classical concept that the impulse-generating machinery is confined to the axon hillock and soma is not supported by our modeling studies, which suggest that the dendrites not only contain active membrane but may play a critical role in shaping impulse frequency. In addition, the presence of the thin axonal segment requires a relatively high density of Na channels to support both ortho- and antidromic impulse propagation; this requirement raises the possibility that the thin segment could serve as the impulse-initiation region. When reasonable channel densities and distributions are established in realistic anatomic representations, the resulting model is capable of generating impulse activity that matches the waveform and frequency versus current (F/I) properties of physiological recordings. Under these conditions, impulse initiation may occur from one of several possible neural districts, and this is particularly evident for stimuli that are near threshold, which often generate an irregular discharge pattern. Thus the possibility of different impulse-encoding mechanisms for different levels of synaptic activation is supported by the modeling results of the present study.

**METHODS**

Experimental methods for obtaining the data on which the modeling results are based are given in the companion paper (Fohlmeister and Miller 1997). Whole cell recordings from a superfused, intact retina-eyecup preparation were used as the physiological metric for judging the success of modeling strategies (see below). The complement of ion channels used in the modeling consisted of four voltage-gated currents (\(I_{Na}, I_{K}, I_{K, A}\), and \(I_{Ca} \)), one Ca-gated (\(I_{Ca} \)), and one leakage conductance. Gating kinetic equations are given in Fohlmeister et al. (1990) and Fohlmeister and Miller (1997). Figure 1A (right) illustrates the flatmount morphology of an intermediate-sized, sustained-on ganglion cell, recorded and stained in the mudpuppy retina with intracellular injection of horseradish peroxidase (HRP). The three-dimensional morphology of this cell was logged onto a computer, using commercially available tools (Eutectic Neuronal Reconstruction System). An ASCII version of the structure was moved to a SUN workstation, where software tools were used to devise a compartmental model of the cell. A schematic Sholl plot of the dendritic branching pattern, with cylindrical representations of different diameter sizes, shows the compartmental representation of the same cell. This cell has processes that form a dendritic tree size of \(\approx 300 \, \mu m\) (calibration bar 100 \(\mu m\)). Figure 1. B–E shows micrographs from different, HRP-stained retinal ganglion cells in the mudpuppy retina to illustrate the shape of the axon and axon-hillock region as well as the thin axonal segment. For all cells, the axon hillock region is a comparatively large structure but becomes very thin a short distance (10–40 \(\mu m\)) from the cell body. The thin region has an average length of \(\approx 75 \, \mu m\) (Carras et al. 1992; Stell and Witkovsky 1973) after which the diameter again becomes larger (Fig. 1F).

Five general models were developed, including equivalent cylinder dendritic models of 1.0, 2.5, and 4.0 \(\mu m\) diam with lengths that varied from 0.25 to 1 mm, a “weak” model, and a “real” model, which was based on the compartmental representation of a
complete dendritic tree morphology described above and given in Fig. 2, top. The weak model was developed to explore the lower limits of channel densities required for repetitive firing and to determine how or whether ortho- and antidromic impulses could develop the classical initial segment-soma dendritic (IS-SD) break in the impulse recorded at the soma (also seen in the EC4 model) as originally proposed by Coombs et al. (1957). The IS-SD break is characterized by a hump in the early rising phase of action potentials recorded in the soma and reflects neural impulse genesis in the neighboring axon hillock compartment; it yields a characteristic signature in phase plots. The weak model is illustrated in Fig. 2 (bottom). In this representation, the hatched compartments, which included the soma and portions of the thin segment and proximal dendrites, contained a reduced density of Na and K channels (Table 1).

The equivalent cylinder models were structured as cylindrically symmetric (Fig. 2). The models were constructed with 400 or 800 sequential compartments, each 15 µm long. The number of compartments comprising cell components are: dendritic cylinder, 35 or 70; soma, 2; initial segment, 3; narrow axonal segment, 6; and distal axon, 354 or 754. A relatively long axon was included to reliably measure impulse propagation velocities, and to provide an “infinitely” long cable structure to reproduce more accurately charging curve parameters and input resistance determinations. The use of a uniform compartment length allowed for simplification of the computer programs.

Our cylindrical soma was of 20-µm diam and 30 µm in length. This yields a soma surface area of 1,885 µm² and a volume of 9,425 µm³. For comparison, a 22-µm-diam sphere has a surface area of 1,963 µm² and a volume of 8,181 µm³. These values are very close to those of a typical recorded cell (cf. Table 1, real cell). Volume plays a role only in connection with the gating of the Ca-activated K channel because that gating is in response to changes in the internal Ca concentration resulting from Ca current. The salient equations are

\[ g_{\text{KCa}} = g_{\text{KCa}} \frac{[\text{Ca}^{2+}]_i/\text{Ca}^{2+}]_{\text{res}}}{1 + ([\text{Ca}^{2+}]_i/\text{Ca}^{2+}]_{\text{res}})} \]

\[ \frac{d[\text{Ca}^{2+}]_i}{dt} = -I_{\text{Ca}}/F - \frac{[\text{Ca}^{2+}]_i - [\text{Ca}^{2+}]_{\text{res}}}{\tau_{\text{Ca}}} \]  

for cylindrical compartments, because the surface to volume ratio is 2/r and the valency is 2 (cf. companion paper Fohlmeister and Miller 1997; Fohlmeister et al. 1990). The Ca-dissociation constant, [Ca^{2+}]_{\text{res}} = 10^{-7} M, and the residual internal Ca concentration, [Ca^{2+}]_{\text{res}} = 10^{-7} M. The integer power in Eq. 1 is j = 1 or 2 (see RESULTS).

The state variables for the ionic conductances of each compartment were integrated using the Euler method with a constant time step. The voltages and longitudinal currents were integrated using the Crank-Nicholson method. The step sizes in both space and time were tested by halving and doubling to ensure accuracy. The integration step was 0.004 ms. All results presented here were confirmed with the program NEURON (Hines 1993), which appeared after the original computer work was completed.

Three elements comprised the modeling strategy: morphology parameters in conjunction with distributions of ion channels were established to provide matches for the frequency versus stimulus (F/I) properties of the most common group (fast) of retinal ganglion cells based on whole cell recording data and constant current pulses injected into the soma; the corollary challenge was to generate models in which impulse waveform closely matched that of the physiological studies by adjusting the variables summarized in Table 1 and using phase plot analysis as the most sensitive index of waveform fidelity; and all models were required to generate impulses that were propagated both ortho- and antidromically to match physiological studies that explored this property of retinal ganglion cells (Carras et al. 1992). However, we emphasize that the physiological data showed sufficient individual variablity, particularly revealed through phase plot analysis, that we did not attempt to exactly match any single spike waveform. We constructed instead a set of models that encompassed the range of the observed physiological variability (Table 1). In the process, the full parameter space was explored with the result that no “secondary minima” (i.e., alternative solutions) were found.

RESULTS

Intercompartmental currents

Figure 3 presents general results for repetitive impulse generation in both physiological whole cell recordings (Fig. 3A) and computer simulations based on three different model assumptions, including a single compartment (Fig. 3B), a 2.5-µm-diam equivalent dendritic cylinder model called EC2.5, and a more realistic compartmental model of a dendritic tree, termed “real” (see Fig. 2) in Fig. 3D. The magnitude of the stimulus current values injected into the soma are indicated (left). Two obvious differences are apparent between the whole cell recording in Fig. 3A and the single-compartment model in Fig. 3B; these include the long trajectory (+) in the physiological response to 10 pA of current and the lower frequency of impulse activity to higher currents. The single-compartment model displays a relatively short trajectory (or latency) to the first impulse to 10
### Table 1. Ionic channel density distributions

<table>
<thead>
<tr>
<th>Model</th>
<th>Current</th>
<th>Regional Conductances (mS/cm²)</th>
<th>Dendrites</th>
<th>Soma</th>
<th>AH</th>
<th>NR</th>
<th>Axon</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC2.5 REAL</td>
<td>( I_{Ca} )</td>
<td>2.0</td>
<td>1.5</td>
<td>1.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>( j = 1 )</td>
<td>( I_{K,Ca} )</td>
<td>0.001</td>
<td>0.065</td>
<td>0.065</td>
<td>0.065</td>
<td>0.065</td>
<td>0.065</td>
</tr>
<tr>
<td>SD* (real) = 21.9 ( \mu )m</td>
<td>( I_{Na} )</td>
<td>25</td>
<td>80</td>
<td>100–150( \dagger )</td>
<td>100</td>
<td>40–70;( \ddagger )</td>
<td>—</td>
</tr>
<tr>
<td>SD (EC2.5) = 20 ( \mu )m</td>
<td>( I_{K} )</td>
<td>12</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>12–18;( \ddagger )</td>
<td>—</td>
</tr>
<tr>
<td>( \tau_{Ca} = 1.5 )</td>
<td>( I_{A} )</td>
<td>36</td>
<td>54</td>
<td>54</td>
<td>54</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>( E_{L} = -60 ) mV</td>
<td>Leak (Real)</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008</td>
</tr>
<tr>
<td>( E_{Na} = 35 ) mV</td>
<td>(EC2.5)</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>ECI.0</td>
<td>( I_{Ca} )</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>( j = 1 )</td>
<td>( I_{K,Ca} )</td>
<td>0.065</td>
<td>0.065</td>
<td>0.065</td>
<td>0.065</td>
<td>0.065</td>
<td>0.065</td>
</tr>
<tr>
<td>SD = 20 ( \mu )m</td>
<td>( I_{Na} )</td>
<td>22</td>
<td>50</td>
<td>70</td>
<td>100</td>
<td>40–70;( \ddagger )</td>
<td>—</td>
</tr>
<tr>
<td>( \tau_{Ca} = 5 )</td>
<td>( I_{K} )</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12–18;( \ddagger )</td>
<td>—</td>
</tr>
<tr>
<td>( E_{L} = -62 ) mV</td>
<td>( I_{A} )</td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>( E_{Na} = 45 ) mV</td>
<td>Leak</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
</tr>
<tr>
<td>Weak</td>
<td>( I_{Ca} )</td>
<td>0.75</td>
<td>0.6</td>
<td>0.6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>( j = 2 )</td>
<td>( I_{K,Ca} )</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>SD = 16 ( \mu )m</td>
<td>( I_{Na} )</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>40/200;( \ddagger )</td>
<td>40–70;( \ddagger )</td>
<td>—</td>
</tr>
<tr>
<td>( \tau_{Ca} = 1.5 )</td>
<td>( I_{K} )</td>
<td>6/12;( $ )</td>
<td>6</td>
<td>6</td>
<td>6/12;( \ddagger )</td>
<td>12–18;( \ddagger )</td>
<td>—</td>
</tr>
<tr>
<td>( E_{L} = -62 ) mV</td>
<td>( I_{A} )</td>
<td>18/36;( $ )</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>( E_{Na} = 45 ) mV</td>
<td>Leak</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>ECI.4</td>
<td>( I_{Ca} )</td>
<td>2.0</td>
<td>1.5</td>
<td>1.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>( j = 1 )</td>
<td>( I_{K,Ca} )</td>
<td>0.01</td>
<td>0.065</td>
<td>0.065</td>
<td>0.065</td>
<td>0.065</td>
<td>0.065</td>
</tr>
<tr>
<td>SD = 20 ( \mu )m</td>
<td>( I_{Na} )</td>
<td>22</td>
<td>80</td>
<td>120</td>
<td>100</td>
<td>40–70;( \ddagger )</td>
<td>—</td>
</tr>
<tr>
<td>( \tau_{Ca} = 1.5 )</td>
<td>( I_{K} )</td>
<td>6–12</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>40–70;( \ddagger )</td>
</tr>
<tr>
<td>( E_{L} = -60 ) mV</td>
<td>( I_{A} )</td>
<td>18–36</td>
<td>54</td>
<td>54</td>
<td>54</td>
<td>54</td>
<td>—</td>
</tr>
<tr>
<td>( E_{Na} = 35 ) mV</td>
<td>Leak</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
</tr>
</tbody>
</table>

| \( I_{Ca} \) and \( I_{Na} \) on the dendrites and of \( I_{K,Na} \) and \( I_{K} \) on the narrow region (NR) of the weak model apply to the four dendritic compartments (60 \( \mu \)m) nearest the soma and to the three NR compartments (45 \( \mu \)m) nearest the axon hillock (AH). The higher values apply to the remaining compartments of the dendrite and NR, respectively. The left column provides additional parameters; \( j \) specifies the exponent in Eq. 1.

* SD, soma diameter. \( \ddagger \) Range tested. \( \ddagger \) Higher values prevent irregular firing near threshold (Fig. 1). § Lower values placed in segments 67–70 (Fig. 1).

### Figure 3

Repellent impulse trains in response to depolarizing current steps of 40, 20 and 10 pA injected into the soma of ganglion cell (A) of the eyecup preparation of the tiger salamander, and models (B–D) identified at the top. The equivalent cylinder model is that of EC2.5 described in the text. Arrows on the 10-pA traces point to the membrane potential trajectories between current onset and first impulse and involve the long latencies associated with cell morphology as discussed in the text. E: phase plots showing equally spaced points (separated by 0.2 ms) of the trajectory of \( \frac{dV}{dt} \) vs. membrane potential, \( V \), of 3 repetitive impulse trains given (left). Trajectory traverses the loop in the clockwise direction and involves a number of circuits, 1 for each impulse, with maximum rate-of-rise \( \approx 200 \) V/s and impulse peak of about +20 mV. Interspike intervals are represented by the nearly horizontal segment (left). Whole cell recording (WCR) data varied somewhat among ganglion cells (cf. Fohlmeister and Miller 1997), and the early rapid falling phase (\( \sim \), bottom right) was not uniformly observed and may be related mechanistically to the slightly lower spike amplitude of this particular cell. The late falling phase (\( \sim \), bottom left) is diagnostic for the magnitude of the calcium current, which was modified for the single-compartment model.
pA of current and generates a higher frequency of impulse activity to the 40-pA current stimulus. These two features, spike frequency to high current and long trajectory to low current, are better matched to the physiology by the simulations of the multicompartmental models illustrated in Fig. 3, C and D. The differences between the equivalent cylinder and real models are relatively minor: both show the long trajectory before the first impulse and both also show a better match to 40-pA current injection when compared with the single-compartment model.

A significant component of this improved match between model and whole cell recording (WCR) data are due to intercompartmental (or “longitudinal”) currents, which spread as a result of current applied to a single compartment of a heterogeneous morphology. The long trajectory always is seen experimentally and virtually impossible to obtain with the single-compartment model. It purely is to be associated with longitudinal currents and geometry and not with channel properties. Simulations show that with the onset of step stimulus current, the membrane potential first changes rapidly at the stimulation site. This local potential change is immediately followed by electrotonic spread to the remainder of the neuron, causing a substantial reduction in the local rate-of-rise of the membrane potential (Hodgkin and Rushton 1952). During this phase, intercompartmental currents dominate the small membrane ionic currents and charge the membrane capacitance of many neighboring compartments. After some time (i.e., latency to first spike), threshold is reached at some point of the neuron, the specific locality depending strongly on the magnitude of the stimulus current for a given neural geometry and channel distribution (see below). On reaching threshold, the membrane becomes highly conductive locally where transmembrane current then dominates intercompartmental (electrotonic) currents. After the impulse has “reset” the membrane, a similar pattern is repeated during the subsequent interspike interval. It is the alternation between spatial influences (electrotonus) in the interspike interval and high transmembrane conductances during impulses that, respectively, control the frequency of impulse activity and maintain the sharpness of spikes.

Phase plot analysis

Phase plots provide one of the best methods for evaluating subtle differences in impulse waveform (Fitzhugh 1969) and have been used to validate the single-compartment models presented in the companion paper (Fohlmeister and Miller 1997). In general, by plotting the time derivative of the voltage trajectory as a function of membrane potential, subtle differences in impulse waveform are appreciated more readily. Figure 3E illustrates phase plots from the physiological study (○), single compartment (△), and equivalent cylinder model records (□) of the records (left). Both the WCR and equivalent cylinder models show a similar peak in the rate of voltage rise (Fig. 3E, top) with some difference in the maximum spike amplitude (dV/dt = 0 at far right). The physiological record shows a somewhat larger early rate of repolarization (→) than the equivalent cylinder model, but both show similar repolarization rates as the impulse waveform continues toward the baseline (−20 to −60 mV). The single-compartment model differs most notably from the other two examples in the repolarization between −20 and −60 mV (left arrow). This region reflects an effect of the large I_{Ca} that was necessary for greater activation of I_{K,Ca} in the single-compartment model to control impulse frequency. In multicompartment models, the magnitude of I_{Ca} was reduced to match the phase plots generated from physiological data. As explained in the calcium section below, the multicompartment geometry takes over much of the control of impulse frequency, a control that had been imposed onto I_{K,Ca} in the single-compartment model.

**Hodgkin-Huxley model**

Although intercompartmental currents (cable properties) are an important feature in the control of repetitive firing, they are not the only factor of a ganglion cell’s ability to generate low-frequency repetitive firing, as may be seen by a comparison with the Hodgkin-Huxley (1952) model. The Hodgkin-Huxley model, which is more appropriate for axons (from which it was derived), responds with high-frequency repetitive firing to any constant suprathreshold current, both in the single-compartment and multicompartment geometries. The minimum frequency for the Hodgkin-Huxley model is ∼50 Hz irrespective of the neural geometry assumed (see Fig. 4), and this property is affected only negligibly when all leakage channels are removed. The present model, in contrast, is capable of low-frequency firing even in the single-compartment version (Fohlmeister and Miller 1997). The resting state of this five-channel model, although stable, is characterized by the property that the membrane potential drifts easily in the subthreshold region in response to small currents (cf. Are ion channels necessary on the dendrites?). The resting state of the Hodgkin-Huxley model,
on the other hand, is relatively more difficult to perturb (i.e., is more conductive in the subthreshold region) and requires much larger currents to obtain equivalent subthreshold changes in membrane potential, both in the presence or absence of leakage conductance.

**Impulse frequency and dendritic cylinder parameters**

Physiological studies of retinal ganglion cells with whole cell recording techniques have revealed a range of F/I relationships, the most common of which are the "fast" cells that typically generate \( \sim 1 \) impulse s\(^{-1}\) \cdot \text{pA}^{-1} \) (Fig. 4). Another grouping consists of "medium" or "slow" cells (cf. Fohlmeister and Miller 1997), which were less common and the impulse discharge rate of which was \(<1 \) impulse \( \cdot \) s\(^{-1}\) \cdot \text{pA}^{-1}. \) Although it is possible that the differences between these cell types relates to variations in the types and distribution of ion channels beyond those considered here, we could reproduce most readily a variation in F/I relationship by changing the diameter of the dendritic equivalent cylinder. Although longitudinal (intercompartmental) currents generate a number of experimentally observed phenomena as given above, the impulse-frequency versus stimulus (F/I) curve of a model with a 1-\( \mu \)m-diam equivalent cylinder dendrite (called EC1 below) remains steeper (Fig. 4) than that for fast cells measured experimentally. Within a given morphology, manipulation of channel densities can be effective in controlling impulse frequency for the smaller stimulus currents \(<25 \) pA) but becomes intractable for larger currents (40 and 50 pA). These high-end F/I properties appear to be uniquely determined by the parameters of the dendritic equivalent cylinder (primarily diameter). Increasing the dendritic cylinder diameter caused a systematic downward shift of impulse frequencies, which included also the low end \( (<10 \) pA) of the F/I curve. In contrast, lengthening of the dendritic cylinder preferentially decreased low-end impulse frequencies with little effect on the higher frequencies. By trial and error, we optimized diameter and length to 2.5 \( \mu \)m and \( \sim 0.5 \) mm, respectively. Thus the EC2.5 model provided the best match to the fast ganglion cells observed physiologically.

For comparison, the typical ganglion cell soma is \( >20 \) \( \mu \)m in diameter with dendritic branching the surface membrane area of which averages some three times the soma surface area and the trunks of which are of \( \sim 2 \) \( \mu \)m diam (tiger salamander). This agrees reasonably well with the geometric parameters of the EC2.5 model. Furthermore, the dendritic branching of ganglion cells does approximate the \((d/d_s)^{3/2}\) power law of Rall (1961), which is the basis for the equivalent cylinder (Fig. 5). The variable electrotonic length (decreasing electrotonic space constant with distance from the soma) implicit in the 3/2 power law when branching occurs was simulated by adjusting (increasing) cytoplasmic resistivity (while simultaneously increasing membrane conductivity). Various patterns of increasing resistivity (and conductivity) with distance from the soma were simulated that yielded small, and only insignificant, differences in the model responses. The electrotonic length of dendritic processes of ganglion cells is of the order of \( l_s^2 \) space constant, again in reasonable agreement with the length of our EC2.5 model equivalent cylinder.

\[
\frac{d_i^3}{d_j^3} + \frac{d_k^3}{d_l^3}
\]

**Determining the distribution of ion channels in the geometric neuron**

When more realistic models of ganglion cells were used in simulations, it was immediately necessary to decide where and to what extent ion channels be represented in different compartments. No experimental data are available on geometric distributions of ion channels in retinal ganglion cells. It was therefore necessary to explore this distribution by trial-and-error simulation. Resolution of possible local, fine-scale variations in channel densities was out of the question. Instead, the neuron was divided into the components of den-
drites, soma, axon hillock (AH), narrow axonal segment (NS), and axon, and the surface membrane of each of these components was supplied with its own, internally uniform complement of channel densities. As indicated below, the full parameter space was explored with the discovery of a single minimum (i.e., agreement with experiment). Table 1 gives these channel density distributions for five morphological configurations. Note that the EC2.5 and real configurations have identical channel distributions (except for leakage, which serves only to establish input resistance homology) and that these are very similar to that of the EC4 configuration. The weak and EC1 models have identical dendritic cylinders and differ essentially only in the reduced channel densities of the weak model. These results suggest that all RGCs, irrespective of class or detailed geometry, contain essentially the same channel density distribution. Although every ion channel, including leakage, when altered to even a small degree, has an impact and will modulate the firing frequency and pattern of the ganglion cell. As a rough approximation, channel densities, with some impurity, may be varied by ~50% from those given in Table 1 (with some notable exceptions); such variation maintains fidelity with the range of firing patterns observed across pools of ganglion cells.

Are ion channels necessary on the dendrites?

Figure 6 (left) illustrates the response of an equivalent cylinder model when all channels (except leakage) were removed from the dendritic compartments. Under these conditions, the impulse rate soared to high levels in response even to low levels (10 pA) of depolarizing current injection. Impulses at the soma diminish some 3 mV in height and rapidly decay away as one moves distally on the dendrite. Figure 6 (right) illustrates the same model in which ion channels as listed in Table 1 were placed in all dendritic compartments. Leakage conductance was adjusted for the model to maintain input resistance homology (cf. Input resistance and charging time). Note that when the dendrites contain voltage-gated ion channels, the impulse rate is reduced and only three impulses were generated by the 10-pA current injection. The phase plots obtained from the soma compartment indicate that the overall impulse waveform is not substantially different under the two modeling conditions (Fig. 6), yet the impact on the repetitive firing rate is quite dramatic. The similarity of the two phase plots, and their near congruence with physiological phase plots, shows again that electrotonic effects are negligible or small locally during the active phase of the membrane. The great difference in impulse frequency, however, points to the importance of generated by the same electrotonic mechanism.

Although every ion channel, including leakage, when altered to even a small degree, has an impact and will modulate the firing frequency and pattern of the ganglion cell. As a rough approximation, channel densities, with some impurity, may be varied by ~50% from those given in Table 1 (with some notable exceptions); such variation maintains fidelity with the range of firing patterns observed across pools of ganglion cells.

leads to the long membrane potential trajectory until threshold is reached for the first impulse. In the absence of excitable ion channels on the dendrite, the charge on the capacitance of the dendritic membrane now acts as a battery, which tends to hold the membrane near the threshold potential of the soma-AH region, which in turn responds with high-frequency firing to the maintained stimulus current. On the other hand, when channels are added to the dendritic membrane, the resulting dendritic active response to every soma impulse causes the accumulated charge on the dendritic membrane capacitance to be bled off (i.e., the dendritic membrane acts as a shunt while active and is reset). Thus the stimulus current must recharge that capacitance after every impulse, and this leads to longer interspike intervals and lower frequency repetitive firing. Thus the interspike trajectory and the long latency trajectory to first spike are generated by the same electrotonic mechanism in the multicompartment models. Herein lies the fundamental difference in frequency control between the single- and multicompartment models; the absence of a geometrically distributed capacitance in the single compartment was compensated by artificially prolonged activation of $g_{K, Ca}$. Such activation, however, requires Ca influx (i.e., an impulse), and therefore it was impossible to generate the long initial latency to first spike with the single-compartment model.

In contrast, the Hodgkin-Huxley model kinetics yield a membrane that is relatively more conductive (or leaky) near the resting potential. Small stimulus currents therefore bleed.
across the membrane, and the minimum stimulus necessary to reach threshold is relatively larger. Suprathreshold stimuli of constant current then lead to relatively high-frequency repetitive firing in the Hodgkin-Huxley model (Fig. 4). Interestingly, the Hodgkin-Huxley model retains its F/I properties with the EC2.5 model geometry even when all channels are removed from the dendrites. This is due to the fact that the transmembrane current of the Hodgkin-Huxley equations dominates longitudinal (electrotetric) current even during the interspike interval because of the high axial (longitudinal) resistance of the neural processes, which are very thin in comparison with the 500-μm-diam giant axon of the squid.

Returning to the present five-channel model, the presence on the dendrites of ligand-gated cationic (or anionic) conductances cannot substitute for the specific voltage-gated channels of the model. (Voltage- and ligand-gated refer here to channels that gate in response to the occurrence of an impulse in the soma, and slower synaptic conductances, respectively.) Simulations in the presence of ligand-gated conductances (and without voltage-gated channels on the dendrites) retain the very high-frequency firing, provided the reversal potential of the ligand-gated currents is at a sufficiently depolarized level (−50 mV or above); a more negative reversal potential for the ligand-gated currents will silence the cell, except for conductances comparable with (or less than) that of \( g_{K_{Ca}} \). These comparisons (i.e., with Hodgkin-Huxley or the substitution of ligand-gated dendritic channels) show that the repetitive firing properties of ganglion cells depend critically on details of the gating kinetics of their channels, particularly in the subthreshold membrane potential range, in addition to the neuron’s morphology and channel density distribution.

**Na channels on the dendrites?**

A dendrite with the density of the three K channels \( (I_K, I_{K_{Ca}}, \text{and} \ I_{K_{A}}) \) plus leakage, as given in Table 1, but without Na channels, will increase the repetitive firing frequencies by some 15–30% with the larger increase occurring at the high-frequency end. (A further substantial frequency increase occurs when Ca channels are reduced or eliminated from the dendrites, see Calcium system.) It may seem surprising that the removal of dendritic Na (and/or Ca) channels should increase the firing frequency. The explanation lies in the fact that when impulses actively invade the dendrites, they cause a substantial increase in the refractoriness of the cell, with its attendant slowing of repetitive firing, and this effect is most pronounced at the high-frequency end of the F/I curve for Na channels (and more uniformly for Ca channels). However, the 15–30% increase in firing frequency is an insufficient effect to rule out the possibility that Na channels may be absent on the dendrites.

Some of the most sensitive analysis regarding the adjustment of channel parameters have come from the evaluation of phase plots, which in turn reflect features during the action potentials. The dominance of local transmembrane current over longitudinal (electrotetric) currents during the impulses has facilitated that analysis but also has proven to be a hindrance for determining the presence of Na channels on the dendrites because of the results stated in the previous paragraph and because of the difficulty of recording intracellularly from the dendrites. Nevertheless, possible bounds on dendritic Na channel density can emerge from considerations of the integrative function of the neuron in response to dendritic (synaptic) stimulation.

**Chaos in retinal ganglion cell discharge**

Retinal ganglion cells respond with an exquisite complexity of a very characteristic type to photic stimulation with constant intensity light pulses (Fig. 7, top). Figure 7, middle and bottom, illustrates the dendritic behavior and the simultaneous soma firing pattern in response to a step current injected into the dendrite of a model in which the diameter of the dendritic cylinder is relatively small (EC1) and the dendritic Na channel density is 22 mS/cm². Similar firing patterns are observed in the dendritic branching real model when stimulated on one or more of its thin processes and with the dendritic Na-channel density in the range of 15–25 mS/cm². These irregular patterns appear to qualify as dynamic “chaos.” In this context, the dynamic responses (repetitive firing), due to the presence of both regenerative
(Na) and recovery (K) channels, endow each compartment with the properties of an oscillator and allow the multicompart-ment neuron to be viewed as a series of tightly coupled oscillators. With adequate dendritic stimulation, the response of this “system” was often nonperiodic, highly irregular, with large differences in the response pattern for very small changes in initial conditions, integration step, or channel densities; the hallmark of dynamic chaos. These phenomena were observed only with a certain range of dendritic Na-channel densities on relatively thin dendritic processes. Specifc features of the characteristic response patterns are strikingly similar to those seen in RGCs with photic stimulation (Fig. 7, top), which suggests a dendritic Na-channel density in the range of \(15 < g_{Na} < 25 \text{ mS/cm}^2\). If the dendritic Na-channel density is too high (i.e., \(g_{Na} > 25 \text{ mS/cm}^2\)), suprathereshold stimuli initiate impulses locally on the den-drite, and the observed characteristic firing patterns are lost, at least with constant dendritic stimulation. When the dendr-itic Na-channel density is \(<15 \text{ mS/cm}^2\), a constant level of dendritic stimulation causes a regular (constant frequency, nonchaotic) impulse train generated in the AH region, with the dendrite “ringing” (i.e., damped oscillation) briefly in response to every soma spike. When Na channels are re-moved entirely from the dendrites, the ringing reduces to a small-amplitude biphasic fluctuation—an electrotonic ef-fect. Remarkably, simulations have shown that Ca channels cannot substitute for Na channels to reproduce these effects, and this appears to be related to both the higher threshold for activation and the absence of inactivation gating in the Ca channels.

\(K^+\) channels are necessary on the dendrites

With Na channels present on the dendrites, even at reduced density, fast voltage-gated potassium channels also must be present, otherwise the RGC will not recover from the depolarization of an action potential; the membrane potential then remains at an intermediate level (−15 to −25 mV, depending on stimulus current). We find that voltage-gated K channels must be present with a minimum density of about half that of the soma to prevent an indefinitely long plateau action potential.

If Na channels ultimately should prove not to be present on dendrites and the characteristics observed above (Fig. 7) be the result of the inherent fluctuation of summing excitatory postsynaptic potentials and inhibitory postsynaptic potentials, then the necessary presence of dendritic voltage-gated K channels already has been established (Fig. 6). Analysis of the RGC models’ responses and comparison with physiological data yield the following likely ranges for dendritic channel densities: \(0 < g_{Na} < 22 \text{ mS/cm}^2\), \(6 < g_K < 12 \text{ mS/cm}^2\), and \(18 < g_{K^+} < 36 \text{ mS/cm}^2\). Furthermore, use of values of \(g_{Na}\) near its upper (lower) limit requires that the dendritic K-channel densities simultaneously be near their upper (lower) limits. Finally, the model results indicate that the channel densities of the more vigorous cells are those given by the upper limit (listed in Table 1). The lower values lead to increased latency to first spike, a steepening of the F/I curve, and some indication of an IS-SD break in phase plots, effects that are sometimes seen in experimental records from what may be cells that are weakened (or dam-aged) in the experimental process. We note therefore that the “ideal” dendrite has a Na-channel density about \(\frac{1}{4}\), and K-channel densities about \(\frac{1}{3}\) of the corresponding densities of the soma region (Table 1).

Channel density in the soma

The soma is the recording site for most data on which the present model is based. The soma is furthermore the site from which the original voltage-clamp data were obtained (Kaneda and Kaneko 1991; Karschin and Lipton 1989; Lipton and Tauck 1987; Lukasiewicz and Werblin 1988) for the identification and kinetics of the model’s channels (Fohlmeister et al. 1990). The soma is also electrotonically small.

Sodium-channel densities on the soma are fixed by the peak magnitude of \(\frac{dV}{dt}\) during the rising phase of impulses in phase plots (Fig. 3E). Potassium-channel (delayed recti-fier, and A-type) densities are assigned to the soma to maintain the shape (in particular, the width or time course) of recorded action potentials. These criteria are considered as critical for the models.

However, the model neuron can maintain repetitive firing with substantially lower channel densities on the soma. The so-called weak model (Table 1) was constructed to explore this phenomenon. This weak model is an extreme case for which channel densities have been reduced to a minimum in a neighborhood of the soma while retaining repetitive firing without substantial distortion of impulses or degradation of the F/I properties (Fig. 4). Several compromises were required: the sodium reversal potential \(E_{Na}\) was increased from +35 to +45 mV, and the peaks of nerve impulses recorded at the soma were reduced from about +20 to about +10 mV. As a result, the maximum \(\frac{dV}{dt}\), as determined from phase plots, was reduced from \(\sim 200\) to \(\sim 100\) V/s for the weak model (Fig. 8). The weak model also requires a somewhat higher \(g_{Na}\) on at least a portion of the axonal narrow segment. This results in the IS-SD break during the early rising phase of spikes in the phase plots, reflecting the fact that the impulses are initiated on the “hot” portion of the model narrow segment. Further reductions in channel densities are not tenable; impulses then become stunted and wide, and repetitive spiking rapidly “washes out.”

Na channels in the narrow segment

After a short initial segment (\(\sim 40\ \mu\text{m}\)), the AH region narrows to a constricted segment of some 60–120 \(\mu\text{m}\) in length (Fig. 1). This constricted segment could be as thin as 0.3 \(\mu\text{m}\); such a restricted size requires a special consideration for the density of ion channels, as thin processes have reduced safety factors created by a small volume-to-surface ratio and a high core resistance. Figure 9 illustrates an analysis with the EC2.5 model together with impulses activated antidromically and recorded at the axonal stimulation site and soma. Antidromic activation of ganglion cell axons results in a normal spike in the soma, indicating that active propagation must occur through the thin segment. We accepted this constraint and discovered that the Na-channel density had to be \(\geq 80\) mS/cm\(^2\) to provide for impulse propagation. Even then, antidromic spike invasion of the soma
are decisive, cell stability is not a factor in setting the upper limit of $g_{V_{Na}}$ there. The EC models continue to remain silent in the absence of stimulation even when $g_{V_{Na}}$ is given a value of several hundred milliSiemens per square centimeter on the narrow segment.

**Axonal ion channels**

Because no voltage-clamp data are available from ganglion cell axons, the actual channel types in this region have not been determined. We model the axon with $I_{Na}$, $I_{K}$, and leakage channels only. The axon nevertheless has a profound impact on repetitive firing behavior—particularly for near threshold stimuli—as detailed below (Fig. 9).

Table 1 gives ranges for axonal Na and delayed rectifier channel densities. (Again, larger or smaller values of the channel densities must be used pairwise.) Simulations with the larger values show stable repetitive firing with a one-to-

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**Fig. 8.** Response of the weak model to 10 and 40 pA of stimulus current into the soma. Note the characteristic of an initial segment-soma dendritic (IS-SD) break ($\rightarrow$) in the phase plots of the 2 records.

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**Fig. 9.** Effect of the higher (left) and the lower (right) axonal channel densities (as given in Table 1) on the response patterns of the EC 2.5 model. **Top:** membrane potential trajectories at the axonal stimulus site (---) and at the soma (· · · ·) in response to an antidromic shock stimulus (2-ms duration) to the neuron at rest. Note the echo spike generated in the plot (right). **Middle:** model responses to just suprathreshold stimulus currents of 1.0 and 4.6 pA injected into the soma (step currents initiated at $t = 0$ ms). Note the long latency to first spike and doublet spiking on the axon only after a transient spiking irregularity associated with the low axonal channel densities (right), and the capability for very low-frequency firing with high axonal channel densities (left). **Bottom:** phase plots for the soma impulse trains of the panels immediately above. Note the IS-SD break observed in the very low stimulus record ($\rightarrow$).
one relationship between impulses recorded at the soma and those propagating on the axon and with the axonal membrane potential returning crisply to near its resting level during the interspike intervals (Fig. 9). When the Na- and K-channel densities are reduced to the lower values in Table 1, a number of intriguing phenomena emerge that are sometimes observed in RGCs. Thus after invading the soma-dendritic region, an antidromically propagating impulse will generate a second impulse on the proximal axon itself, which then propagates orthodromically (Fig. 9, top right). Seen from the distal stimulation site on the axon, this second spike appears as an echo (or reflection) of the first, antidromically propagated impulse. Thus the axonal membrane (near the narrow segment) has remained suprathreshold after the antidromically invading spike. After generating the echo spike, the axonal membrane potential returns crisply to near its resting value, and the neuron remains silent.

Very low frequency repetitive firing properties also are affected by axonal channel densities. The smaller values of those densities (Table 1) correspond to a threshold stimulus level for repetitive firing of approximately 4.5 pA. Related to the echo spike phenomenon is a double spiking on the axon that occurs for near-threshold stimuli to the soma (Fig. 9, middle right). The impulses of each doublet are initiated at different locations within the trigger zone; the first is triggered just beyond the narrow segment on the axon and does not invade the soma, whereas the second is triggered in the AH—narrow region and is recorded almost simultaneously at the soma. Note that only one soma spike may be recorded for each doublet on the axon. Such double spiking may be useful to the ganglion cell by enhancing signal transmission under very low light conditions (i.e., near threshold for ganglion cell activation). Use of the higher axonal channel densities (Table 1), threshold stimulus for repetitive firing drops to near 0 pA, and the EC2.5 model is capable of relatively stable impulse frequencies of <1 impulse/s (Fig. 9, middle left).

**How are impulses generated in multicompartment models?**

Morphological studies that attempted to localize ion channels have demonstrated a higher, less mobile collection of Na channels in the AH region of the cell (Wollner and Catterall 1986). On the other hand, at least some whole cell recordings from ganglion cells tend to show variance in impulse waveform and amplitude behavior that is not inconsistent with some variability in the site of spike initiation. The EC2.5 model shows a pattern in which the impulse initiation site moves more distally from the soma as the stimulus level is reduced, particularly for the lower channel densities in Table 1. Thus the soma-hillock region is the trigger zone with 40 pA of stimulus current, whereas with 10-pA the impulse reaches its peak first on the narrow segment. Remarkably, as the stimulus level is reduced to near the threshold for repetitive firing, impulses actually may be initiated on the axon beyond the narrow segment. With the lower axonal channel densities in Table 1, and for stimulus currents in the range of 4.5–10 pA, the repetitive firing frequency becomes irregular, and the impulse initiation site “jumps around” between the axon and the narrow segment during the irregular spike trains thus generated. Double spiking also may occur, as noted above. A variable IS-SD break appears in the phase plots (Fig. 9) of these low-frequency spike trains that is more pronounced for those impulses initiated more distally from the soma. Figure 10 illustrates the spatial differences for impulse initiation with the EC 2.5 model. In the example in Fig. 10, top, a 10-pA current was injected into the soma and recordings were obtained for the soma, AH, dendritic compartment, narrow region, and distal axon. The expanded recording in Fig. 10, top right, shows the compartmental timing and source of impulse initiation. The soma and AH are virtually indistinguishable and initiate the impulse. However, because of the comparatively high density of Na channels in the narrow region, this compartment also initiates an impulse, the peak of which occurs before that of the soma-AH impulse. With some delay, the impulse propagates into the dendritic tree. The dendritic impulse has a lower rate-of-rise due to the smaller density of Na channels in these compartments. Figure 10 (bottom) illustrates impulse initiation in the same model when the stimulus (10 pA) is applied to a central dendritic compartment (35). In this example, the impulse also is triggered in the soma-hillock—narrow segment area, after which the impulse propagates back into the dendritic tree. A better visualization of this sequence is illustrated Fig. 10, bottom right. Note that the impulse on the narrow region decays more slowly than that of the dendrites or S-AH because this region has a relatively lower K:Na channel density ratio. This model, which closely matches the performance of retin
nal ganglion cells, also conforms to the ideas recently advanced by Stuart and Sakmann (1994) for pyramidal cells. Thus even though the dendrites contain voltage-gated ion channels, including Na channels, the impulse is initiated in the soma-hillock—narrow segment area when stimuli are applied to the soma or dendrites. This result is predicted because of the differential Na-channel densities distributed into each of the critical compartments.

In this connection, it is interesting to note that a simulated sustained plateau action potential on the soma in response to current stimulation can cause high-frequency repetitive firing on the axon because of the partial decoupling of the soma region from the axon by the presence of the narrow segment. These high-frequency impulses then are propagated faithfully on the axon and cause a small-amplitude rippling superimposed on the plateau potential at the soma. This is, of course, an artificial phenomenon, because the plateau does not occur in the experimental data and requires substantial channel-density reductions in the soma-dendritic region. Nevertheless this degree of decoupling—due to the narrow segment—does suggest that the spike train seen at the soma may not always be an absolute representation of the transmitted impulse train on the axon, and this is particularly so for near threshold stimuli.

**Weak model**

Our recordings from retinal ganglion cells occasionally show a prominent IS-SD break, and an earlier study using antidromic optic nerve stimulation provided an explanation, similar to that of Coombs et al. (1957) in retinal ganglion cells (Carras et al. 1992). It is now clear, however, that most retinal ganglion cell recordings obtained with whole cell electrodes do not typically show the IS-SD break phenomenon. This is reflected by our EC2.5 model for which the two neighboring compartments of AH and soma fire in near synchrony (Fig. 10). However, the weak model (cf. *Channel densities in the soma*) does generate a prominent IS-SD break without seriously compromising the ability to satisfy the F/I properties of the cell. The peak rate-of-rise of the action potentials is halved (Fig. 8, phase plot) to 100 V/s, and it is worth noting that all recordings from RGCs that exhibited an IS-SD break also showed a similarly reduced peak rate-of-rise in their action potentials. In the weak model, the impulses generated by a 10-pA current injection show a more prominent shoulder on the rising phase, marked by the arrow on the phase plots of Fig. 8. This IS-SD shoulder becomes less prominent but still evident when a higher rate of firing is achieved by an injection of 40 pA into the soma compartment, and this again reflects the moving trigger zone described above in which impulse trains initiated with larger stimuli arise more proximally to the soma. It is also worth emphasizing that a prominent shoulder on the soma spike can be seen when dendrites generate impulses that precede the soma spike, so that the mere appearance of a shoulder on the soma spike does not guarantee an AH origin (Fig. 11). The latter is ensured, however, when antidromic impulses are initiated on the axon and the impulse waveform is evaluated at the soma.

Figure 11 illustrates the variable spike origin in the weak model. A 10-pA stimulus applied to the soma evoked impulses that begin in the narrow segment, followed by one in the AH, soma, and dendrite. Again, this model also propagates the impulse into the axon. The impulse generated in this soma-hillock region propagates into the narrow region and conveys a shoulder on the repolarization phase of the impulse there.

**Spiking dendrites?**

Figure 11 (bottom) illustrates the response of the weak model when the same stimulus (10 pA) is applied to a central dendritic compartment. Under these conditions, an impulse is generated first in the dendrites, which then propagates toward the soma, where the impedance mismatch causes active impulse failure and passive spread of impulse current into the soma. As the dendritic spike decays passively into the soma, it activates, with some delay, an impulse that begins in the soma (expanded scale at right), followed rapidly by an impulse in the axon hillock and narrow regions. The impulse generated in the narrow region peaks before that in the soma-hillock region because of the higher density of Na channels there. Note that this form of stimulation also provides an impulse in the axon. Thus independent dendritic impulse activity is a possibility when the dendritic Na-channel density begins to rival that in the soma and AH as it does in the weak model.

**Fast, medium, and slow ganglion cell discharge**

Physiological studies of retinal ganglion cells, based on whole cell recordings, showed that most recorded units could...
be described as fast, for which the rate of impulse discharge was \( \sim 1 \text{ Hz/pA} \). However, a number of cells fell to intermediate and lower discharge rates, and these units were termed medium and slow (Fohlmeister and Miller 1997). Cells that fell into the last group were often difficult to evoke any discharge with low to intermediate levels of current. In Fig. 4, the physiological F/I relationship of fast cells is well matched by both the real model and the EC2.5 model. In contrast, the EC4 model shows a much reduced F/I curve and is comparable with the slow group defined in the previous paper. With the channel densities listed in Table 1, the impulse frequency of EC4 is 21 imp/s, and quite regular, with 40 pA of stimulus. Spiking becomes somewhat problematic (depending somewhat on axonal channel densities) when the stimulus is reduced to 10 pA; an irregular impulse train of \( \sim 4 \text{ imp/s} \), showing a variable IS-SD break, occurs after a latency to first spike of nearly 600 ms. Impulses broaden slightly for all levels of stimulus, showing a peak rate-of-rise of \( \sim 150 \text{ V/s} \) in phase plots of the soma record. With dendritic channel densities reduced to \( g_{\text{Na}} = 6, \ g_{\text{K}} = 18 \text{ mS/cm}^2 \), the EC4 model remains subthreshold with 10 pA and fires at 37 imp/s with 40 pA of stimulus. The phase plot shows a peak rate-of-rise of \( \sim 130 \text{ V/s} \). Use of the higher dendritic channel densities (those listed in Table 1) therefore yield the best comparison with the behavior of slow and medium RGCs; the upper frequency range agrees well, and slow RGCs commonly were found to fire irregularly—or to cease impulse activity altogether—for the lower stimulus range (Fohlmeister and Miller 1997).

### Calcium system

For purposes of this paper, we define the calcium system as all cellular components and functions related to the calcium and Ca-activated potassium currents. Given the relatively small conductances associated with these two channels (\( g_{\text{Ca}} \) and \( g_{\text{K,Ca}} \) lie in the range of \( <2.0 \text{ mS/cm}^2 \)), they are remarkable both for their large effects on the impulse train responses and for the accuracy with which the channel densities can be determined with the tools at our disposal.

The single-compartment model (Fohlmeister and Miller 1997) was constructed to approximate the F/I properties of RGCs as closely as possible within the space-clamp constraint implied in such modeling. To approximate the F/I curve within that constraint, calcium current was increased, and the gating of \( g_{\text{K,Ca}} \) was controlled closely by adjusting (distorting) the removal time of cytoplasmic calcium to \( \tau_{\text{Ca}} = 50 \text{ ms} \) for the single-compartment model.

In the multicompartment models, much of the control of the F/I properties is taken over by the parameters of the morphology, as shown above. Nevertheless, \( I_{\text{K,Ca}} \) retains its fundamental role in stabilizing the cell electrically (i.e., in preventing spontaneous firing), as well as lengthening the interspike intervals for all levels of stimulus. However, when cell morphology is considered, the gating of \( g_{\text{K,Ca}} \) becomes unimportant for tonic impulse frequency control, and the channel appears to act principally as a slowly modulating potassium current. As such, it may well be responsible for at least some of the adaptation seen in RGCs when stimulated with step currents in the soma. A role of \( g_{\text{K,Ca}} \) in adaptation even may be considered likely because the instantaneous impulse frequency is highly sensitive to the magnitude of \( g_{\text{K,Ca}} \) (cf. Fohlmeister et al. 1977 for the role of the electrogenic Na/K pump in adaptation, which reflects another ion accumulation effect, that of internal Na). Lipton and Tauck (1987), show only a fivefold increase in \( g_{\text{K,Ca}} \) with a Ca concentration change from 0.2 to 18 \( \mu \text{M} \). This finding favors use of \( j = 1 \) in Eq. 1, which was employed in constructing the EC models and for which the corresponding conductance change is a factor of 5.7. (This conductance change is a factor of 26 with use of \( j = 2 \).) Nevertheless, fast gating properties of the channel were retained (cf. Eq. 1), and we find the best reproduction of the interspike membrane potential trajectories with \( \tau_{\text{Ca}} \) in the range of 1.5–5 ms, which leads to adjustments in the early portions of interspike intervals only. These brief times are probably much too short to reflect mechanisms for the sequestering and removal of cytoplasmic free Ca\(^{2+}\) (Cannell et al. 1987; Hernandez-Cruz et al. 1990; Tank et al. 1988) and may reflect instead a component of electrical gating of \( g_{\text{K,Ca}} \).

Time constants in the range of 1.5–5 ms are typical for voltage gating, and \( g_{\text{K,Ca}} \) has been shown to gate in response to large depolarizations, such as occur during impulses (Barrett et al. 1982; Marty 1981; Maruyama et al. 1983; Pallota et al. 1995). We note in passing that Lipton and Tauck (1987) also find that \( g_{\text{K,Ca}} \) has the largest single-channel conductance (115 pS in physiological solutions) among the complement of channels of RGCs.

Unlike \( I_{\text{K,Ca}} \), the calcium-current, \( I_{\text{Ca}} \), provides a strong signature in phase plots, which analyze processes during the impulse. As with the single-compartment model, note in Fig. 12 (phase plot) that the Ca current is manifest in two regions of the plots: near the peak of the action potential and during the latter part of the falling phase of action potentials. Note also that the impulse frequency increases when either \( g_{\text{K,Ca}} \) or \( g_{\text{Ca}} \) are blocked (cf. Fohlmeister and Miller 1997).

Because cell morphology potentially allows highly nonuniform channel density distributions, we explored the effects of manipulating calcium and sodium channel densities on the dendrites. Figure 13 gives a spike train in response to 40 pA injected into the soma of the EC2.5 geometry, but with \( g_{\text{Na}} = 0 \) (down from 22 mS/cm\(^2\)) and \( g_{\text{Ca}} = 6 \text{ mS/cm}^2 \) (up from 2.0, see Table 1) on the model dendrite. Under these conditions, the impulse frequency response is depressed strongly, and the cell remains silent with 10 pA of stimulus (not shown). The dendritic calcium spikes are relatively wide and exhibit the strong Ca signatures in their phase plot (Fig. 13).

When the channel-density manipulation is carried to an extreme, with \( g_{\text{Na}} = 0 \) and \( g_{\text{Ca}} = 30 \text{ mS/cm}^2 \) on the dendrites and with \( g_{\text{Na}} = 20 \) and \( g_{\text{Ca}} = 20 \text{ mS/cm}^2 \) on the soma (but with AH, narrow segment, and axon densities unchanged), the soma ceases to spike for any level of soma or dendritic stimulation, although impulse trains still are generated on the narrow segment and propagated on the axon. The cessation of soma spiking is due to the low Na-channel density there, and shows that Ca channels do not readily substitute for Na channels for this function.

### Voltage-gated potassium channels

The ratio \( g_{\text{Na}}:g_{\text{K}} \) of 3:1 that was previously established for the single-compartment model was retained for the dendrites,
soma, AH, and narrow segments of the EC models. This ratio serves the purpose of maintaining the impulse waveform in these multicompartment models. Nevertheless, it is instructive to determine the relative contributions of these two currents to features of the model impulse trains. Figure 14 gives impulse trains and corresponding phase plots in which the relative weighting has been shifted in favor of one or the other of the two channels. Increasing the weight in favor of $g_{K}$ at the expense of $g_{A}$ has the following pronounced effects: 1) the latency to the first spike is increased; 2) the postspike undershoot is decreased, thus making the impulse record appear to be somewhat elevated in membrane potential, and the impulses widen; 3) furthermore, the threshold current for repetitive firing is increased; and 4) the subsequent F/I curve steepens, so that the impulse frequency with 40 pA is higher than that for the standard EC2.5 model.

Note that $g_{A} = 0$ shows both the reduced impulse peak and an effect during the latter half of the falling phase that is strongly diagnostic for the absence of Ca current (see text).

**Input resistance and charging time**

The gated channels alone (without leakage) are fully adequate to reproduce the F/I and phase plot properties of RGC repetitive firing. However, when this model cell (without leakage) is presented with a hyperpolarizing current, it yields an input resistance of $\sim 2.3 \, \Omega$ with a time constant of nearly 200 ms. The experimental value of $\sim 1-1.2 \, \Omega$ is achieved by including a leakage conductance of $\sim 0.005 \, \text{mS/cm}^2$. Although slightly more sensitive to the value of the leakage reversal potential, $g_{L}$, than the single-compartment model, this parameter for the geometric model can be chosen in the neighborhood of $-60 \, \text{mV}$. Figure 15 gives a plot of input resistances, $R_N$, and time constants $\tau$ for charging curves, as well as the effect of leakage on the resting potential, $V_{R}$, of the EC2.5 model for values of $0 \leq g_{L} \leq 0.01 \, \text{mS/cm}^2$.

**DISCUSSION**

The inclusion of five different ion channels into a model for impulse generation has provided the best account yet available to explain how retinal ganglion cells generate low-frequency repetitive firing. The presence of each of these ion channels was established experimentally (Kaneda and Kaneko 1991; Lasater and Witkovsky 1990; Lipton and Tauck 1987; Lukasiewicz and Werblin 1988), and rate-
Thus we consider the EC2.5 model to represent the most common fast RGCs; indeed the EC2.5 and real models proved to be interchangeable and provided a good match for these cells, the F/I relationship of which is \( \sim t \cdot \text{impulse} \cdot \text{s}^{-1} \cdot \text{pA}^{-1} \). On the other hand, the EC4 model represents the more rare slow RGCs, which display a number of irregularities in their firing responses and suggests that slow cells are characterized by relatively larger diameter dendritic trunks. The EC1 model was constructed to reproduce the ‘chaos’ response perhaps seen physiologically; it requires stimulation of thin synaptic processes (the numerical designators 1, 2.5, and 4 of the EC models denote the equivalent cylinder diameter in micrometers). The weak model was constructed to explore the acceptable lower limits of channel densities in the “encoder region.” It has been our experience that experimental manipulation of individual neurons can cause a fraction of the excitatory channels to become nonfunctional (e.g., Fohlmeister et al. 1977, where it was found that the encoder function fails before loss of generator potential or input resistance during long experimental sessions). We therefore wished to explore possible artifacts related to experimental trauma and to determine the safety factor built into healthy cells.

Although the principal aim of this study was the construction and testing of realistic ganglion cells, the results presented here have deeper and broader implications for electrical processes of central neurons in general: the nature of model impulse trains, and electrical activity in general, depends exquisitely on the leakiness that results from the electrically gated channels themselves in the subthreshold region. Historically such channels were judged by their ability to generate action potentials (e.g., the Hodgkin-Huxley model). The extrapolation of the voltage dependence of the model rate constants into the subthreshold region generally was assumed to be of less importance because that voltage range involves only a relatively very small percentage of

\[
g_{k} = 108 \text{mS/cm}^2, \quad g_{A} = 0 \\
g_{k} = 24 \text{mS/cm}^2, \quad g_{A} = 0
\]

FIG. 14. Impulse trains generated with 40 pA of stimulus current in the EC 2.5 model soma with the delayed rectifier channels replaced by additional A channels \((g_{k} = 0, g_{A} = 108 \text{mS/cm}^2, \text{top left})\) and with the A channels replaced by additional delayed rectifier channels \((g_{k} = 24, g_{A} = 0 \text{mS/cm}^2, \text{bottom left})\). The corresponding phase plots are superposed on the right for a direct comparison. See text for interpretation and additional neural effects.

\[R_{N}V_{\text{Rest(t)}} \text{ vs } Q_{L}\]

FIG. 15. Resting potential at the soma, \(V_{\text{rest}}\), input resistance, \(R_{N}\), and charging time constant, \(\tau_{\text{c}}\), as functions of the leakage conductance, \(g_{k}\), in the EC 2.5 model. The resting potential of the (distal) axon may vary somewhat (±2 mV) from that of the soma, and this depends on the axonal channel densities (Table 1). Input resistance and time constants were determined with hyperpolarizing current steps injected into the soma and a peeling procedure to separate components of the charging curve; \(\tau_{\text{c}}\) was determined as the slowest time constant in this procedure.
the gating range of the channels. However, the levels (or magnitudes) of membrane current associated with action potentials, and those associated with the encoding (i.e., spacing) of those same action potentials, differ by several orders of magnitude. This places a twofold demand on the accuracy of the voltage dependence of the rate constants: they must generate an accurate waveform for action potentials as determined in phase plots and they must extrapolate into the subthreshold region so as to generate current levels comparable with those of the lowest levels of suprathreshold stimulus current. All membrane current components (those from gated channels, leakage, and stimulus) must be of the same order of magnitude throughout most of the interspike intervals, if they are to produce nearly linear F/I curves such as those observed for ganglion cells. If a gated channel were to produce a relatively large membrane current in the interspike interval, then stimulus current must be comparably large to "move" the membrane potential in the face of the large channel current, and any additional small leakage current becomes virtually invisible. Thus a fundamental difference between the five-channel model used here and the Hodgkin-Huxley model is reflected in the relative magnitudes of the respective leakage conductances of ~0.005 and 0.3 mS/cm², a difference of (about) two orders of magnitude. This reflects the large difference in F/I properties between the two models (Fig. 4).

Indeed, this large change in the present model from the Hodgkin-Huxley model is responsible for the host of phenomena observed herein. Capacitative charging, being the same for all membranes, is therefore relatively much more important here. With the much reduced leakage, the capacitor holds its charge much longer and supports an earlier finding of the importance of a large "effective capacitance" from a systems analysis of repetitive firing (Fohlmeister et al. 1977) carried out in the crayfish stretch receptor, muscle spindle, and Limulus ommatidia. The concept of membrane capacitance as a "battery" (or more suggestively, accumulator) allows a small stimulus current to charge that battery, which leads to the long latency to first impulse seen during low-frequency repetitive firing (Fig. 3). The battery (capacitance) holding its charge allowed us to determine the presence of gated channels on the dendrites (Fig. 6). The active response of these channels does "reset" the capacitor (battery), which therefore must be recharged between impulses to generate low-frequency firing with appropriate (low) levels of stimulus current. The charge on the distributed capacitor allows for a potentially surprising variety of phenomena, including a number of forms of irregular impulse trains, and even mathematical chaos can be demonstrated with the right level of dendritically distributed ion channels (Fig. 7). Other phenomena that are evident, particularly when stimulus current is near threshold, include the production of impulse pairs (Fig. 10, 4.6 pA). Under certain conditions, impulse pairs are clearly evident on the axon, whereas the soma recording shows a single full blown spike together with a small impulse passively propagated from the axon: the first member of each doublet is initiated on the axon beyond the narrow segment, followed by a second impulse initiated on the narrow segment itself. Only the second impulse of each doublet is recorded at the soma; the first impulse of each pair may be observed as a passively propagated (aborted) impulse into the soma. These doublets are seen with either soma stimulation or low-level dendritic stimulation. If this modeling behavior occurs in retinal ganglion cells, one may speculate that its purpose is to enhance the transmission of signals (by doubling the number of propagated action potentials) under low-stimulus conditions and thus magnify the ganglion cell response for conditions near threshold. As the stimulus level is increased, doublet spiking becomes intermittent before the one-to-one soma-axon spiking occurs.

The modeling results of this study have raised the possibility that the site of impulse generation may not be rigidly fixed: it is possible then that spiking neurons may be considerably more flexible in their integrating function than previously assumed. More experimental detail to impulse trains and spike waveform may help to determine whether this type of situation is observed physiologically, but we already have seen some phenomena in impulse trains, based on whole cell recordings, which are at least suggestive of this possibility. The modeling results of this study show that retinal ganglion cells, and by extension other CNS neurons, have the potential for a repertoire of integrating and signaling functions the breadth of which may have been underestimated in the past and certainly must be a subject of investigation for the future.

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REFERENCES


