The Rhythmic Consequences of Ion Channel Stochasticity

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Ion channels are membrane spanning proteins with central pores through which ions cross neuronal membranes. The pores through each ion channel flicker between open and closed states, starting and stopping the flow of ions and the electrical current they carry. Hence the current flickers on and off, varying widely on very short time scales. Recent evidence suggests that this noisy current is a source of rhythmic behaviors in neurons. In this update, we begin by providing an illustrative model that links the stochastic flicker of ion channels to neuronal rhythms. The authors explore recent experimental work that shows channel flicker is necessary for at least one rhythm that characterizes a class of cortical neurons in vitro. Finally, the authors highlight a number of novel studies that link ion channel stochasticity to neuronal rhythmic behaviors in other interesting ways. NEUROSCIENTIST 12(5):**1–7**, 2006. DOI: 10.1177/1073858406290793

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Stochastic molecular interactions enable many macroscopic cellular behaviors. In growing recognition of the importance of stochastic interactions, researchers are beginning to explore their effects in a host of cellular processes. In *Escherichia coli*, stochastic transcription of a single molecule of β-galactosidase triggers bursts of protein production (Cai and others 2006). In a *Xenopus* oocyte model, stochastic gating of IP_3 receptors triggers Ca^{++} release from internal stores, initiating Ca^{++} waves (Keener 2006). More specific to neurons, Na^+ channel flicker enables a plentiful range of stochasticity-dependent behaviors. Na^+ channel stochasticity blurs the distinction between trains of isolated spikes and Ca^{++}-dependent bursts (Rowat and Elson 2004), places structural limits on neuronal anatomy (Faisal and others 2005), constrains spike timing reliability (Schneidman and others 1998), and enables regular membrane potential oscillations (Dorval and White 2005). In this update, we use a simple model of Na^+ channel stochasticity to illustrate how it may generate macroscopic neuronal effects, and we review recent experimental and theoretical work that highlights its biophysical importance.

In 1952, Hodgkin and Huxley published the first electrophysiological description of action potential propagation. Although the quantitative details differ across species and neuronal classes, five decades of experimental examination have revealed a near universality of Hodgkin and Huxley's description. Electrical spikes in membrane potential reflect a chemical battle for ion permeability, or ion conductance, dominance. At least one positive ion species, typically Na^+, whose flow depolarizes the membrane, must have a conductance that increases with depolarization. A spike begins with a slight depolarization that increases the conductance to a Na^+, which is more highly concentrated in the extracellular space than in the neuroplasm. The increased conductance enables Na^+ to rush down its concentration gradient into the neuron, further depolarizing membrane potential, which further increases conductance, and so on, into a full-blown action potential.

In their construction, Hodgkin and Huxley assumed that membrane potential and conductance were smooth, continuous functions of space and time. Although this assumption holds for potential, subsequent findings have shown that the lipid membrane itself is ion impermeable. Ionic concentrations are not smooth quantities diffusing across membranes en masse. Individual ions traverse the membrane one at a time through tiny selective channels in membrane spanning proteins. There are only so many of these *ion channels* in any patch of membrane, and they can be either open or closed. Each channel has a fixed conductance when it is open and zero conductance when it is closed. Even if the ion channels were distributed as smoothly as possible in the membrane, which they are not, a channel opening or closing in a small patch of membrane causes the conductance to change abruptly.

How Channel Noise Can Create a Rhythm

A Na^+ channel protein can be conceptualized as a pathway with a series of gates (Fig. 1*A*). The gates can be open, in which case, Na^+ ions rush down the path into the neuron, or closed. Spanning the membrane, a channel protein is continuously battered about by thermal collisions with

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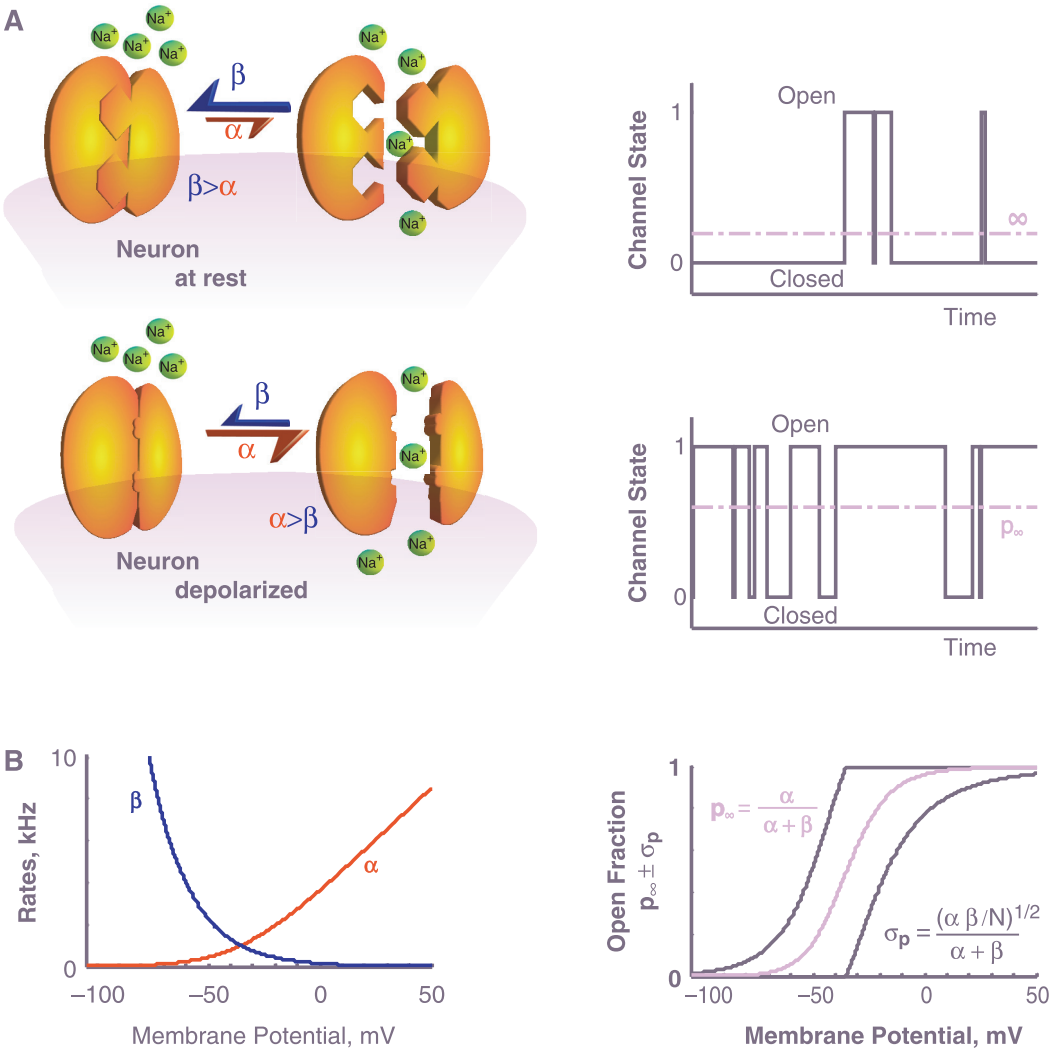

Fig. 1. Simple Na^+ channel. A cartoon representation of an Na^+ channel flickering between open and closed states. *A*, At rest (*top*), the closing rate constant β is much larger than the opening rate constant α. Although the channel is constantly flickering between open and closed states, $\beta > \alpha$ means the channel will be closed more than open. As the membrane is depolarized (*bottom*), α exceeds β and the channel spends more time open. *B*, Rate constants (*left*), as a function of membrane potential, that Hodgkin and Huxley fit to experimental data taken from the squid giant axon. The rate constants combine to determine the average (p_∞) and standard deviation (σ_p) of channel state (*right*) via the displayed equations. The graph depicts $p_\infty \pm \sigma_p$ when the number of channels N equals 1. For p_∞ near 0 or 1, σ_p is small; for moderate p_∞ (i.e., $0.1 < p_\infty < 0.9$), σ_p is large, meaning that the channel state over some small window of time can deviate significantly from the average channel state.

molecules on either side. These collisions knock the ion channel back and forth, opening and closing the gates. The rate at which each gate is expected to open or close is a membrane-potential-dependent quantity labeled α or β, respectively. Near rest, the gates close much faster than they open ($\beta > \alpha$) and the channel spends most of its time closed. As the membrane depolarizes, however, the gates open sooner and close later ($\alpha\uparrow$, $\beta\downarrow$) and the channel spends more and more time open. If the membrane potential has been held constant for a long time, the probability that each gate is open is $p_\infty = \alpha/(\alpha + \beta)$.*

We have just described p_∞ as the open probability of each channel. In the Hodgkin and Huxley construction, however, p_∞ is the average fraction of open channels. These two descriptions are functionally equivalent—if the probability of any channel being open is one half, then on average one-half of the channels will be open. However, the Hodgkin and Huxley construction does not allow for channel state deviations from p_∞. In reality, the actual average state p of all channels in a neuron, although approaching p_∞ on average, may be forbidden from ever reaching p_∞ exactly. Imagine a neuron with only one Na^+ channel and $p_\infty = 0.5$. At any moment in time, that channel can be opened or closed; it can never be half open.

In actuality, p bounces around its mean with some standard deviation σ_p defined in Figure 1, where *N* represents

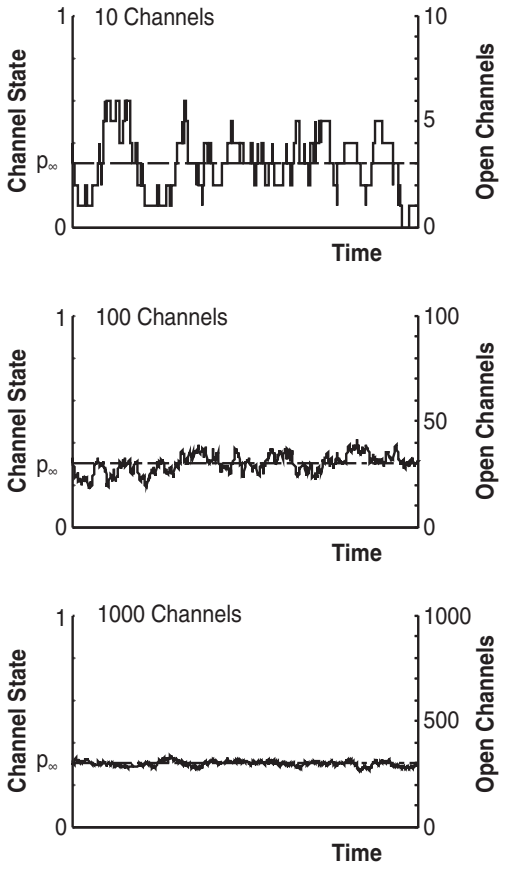

Fig. 2. Na^+ channel flicker. The channel state deviation decreases with increasing channel number. Rate constants α and β were set such that p_∞ equaled 0.3 (*left* axes). Three simulations were run on membranes that included 10 (*top*), 100 (*middle*), and 1000 (*bottom*) channels, such that the average numbers of open channels were 3, 30, and 300, respectively (*right* axes). Fluctuations in p visibly reduce as channel number increases.

the number of Na^+ channels. The more channels in a neuronal membrane, the smaller the deviations, and the closer p stays to p_∞ (Fig. 2). In the limit of an infinite number of channels, the standard deviation goes to zero, and the Hodgkin and Huxley description suffices. The question we address in this update is whether finite numbers of Na^+ channels have functional consequences, or whether biophysically, σ_p is always too small to matter.

To address this question conceptually, we must understand something about the mathematical structure of neuronal behavior. We turn to a simple circuit model of a neuronal membrane, based on the Hodgkin and Huxley description (Fig. 3*A*). The lipid bilayer membrane is modeled as a capacitor separating the neuroplasm from the extracellular space. In parallel with that membrane are channels through which Na^+ and K^+ ions can flow. Associated with each ion species is a Nernst potential (V_{Na} and V_K) and a maximum conductance (G_{Na} and G_K)—the effective conductances when all of the channels of a given type are open. The actual conductance to a given ion is its channel state times the maximum conductance (e.g., pG_{Na} for Na^+).

As described above, p_∞ changes with membrane potential redrawn here as the black line in the top-right of Figure 3*A*. From the circuit diagram (holding s constant), we calculate the steady-state membrane potential V_∞ as a function of p, drawn in purple on the same plot in Figure 3*A*. The curves intersect at three *fixed points:* points at which, in the absence of noise, p and V_m will stay *fixed*. Two of these points (closed circles) are stable, meaning that if p or V change a little bit, the system will evolve back to the fixed point. The other fixed point (open circle) is an unstable threshold, meaning that if p or V_m change a little bit, the system will shoot away from the point. For example, imagine the system sitting at the unstable fixed point when some noise knocks p up a tiny bit. From the curves, we can see that a larger p yields a larger V_∞ and so V_m increases to the new V_∞. The new, higher V_m yields a higher p_∞ and so p increases to the new p_∞. This positive feedback loop continues until the system reaches a stable fixed point, at V_{peak}.

Broadly speaking: If V_m is below threshold (V_{th}, green), it will evolve back to rest (V_{rest}, blue); if V_m is above threshold, it will evolve to a peak potential (V_{peak}, red). The lower two plots of Figure 3*A* each show five example traces of membrane potential, when the number of Na^+ channels in the neuron is 100 (*top*) or 1000 (*bottom*). The fixed points are unchanged by the number of channels, but the channel-flicker-induced deviations from V_{rest} are much greater with fewer channels. In the 100-channel simulations, deviations from rest eventually drive V_m over threshold, whence it quickly shoots to V_{peak}, never to return.

Fortunately, V_{peak} is not a biophysically permanent condition. In the Hodgkin and Huxley construction, Na^+ channel inactivation collaborates with K^+ channel activation to reset membrane potential. For simplicity here, we ignore the effects of Na^+ channel inactivation. From the circuit model, s quantifies K^+ channel state as p quantifies Na^+ channel state. From the Hodgkin and Huxley construction, the K^+ channel rate constants behave similarly to the Na^+ rates, but universally more slowly. The net result is that s changes much more slowly as a function of membrane potential than p.

For any fixed value of s, we can calculate $V_\infty(p)$ (Fig. 3*B*, *top-left*). Plotting those lines against $p_\infty(V_m)$ we see that the nature of the V_m-vs-p relationship depends on s. For moderate values of s, the system is qualitatively similar to the example in Figure 3*A*: two stable and one unstable fixed points. However, for very high s (e.g., 0.9), the lines never intersect near V_{peak}, there is no threshold, and the only fixed point is at V_{rest}. Conversely, for very low s (e.g., 0.1), the lines never intersect near V_{rest}, there is no threshold, and the only fixed point is at V_{peak}. These relationships enable membrane potential to recover from a peak. If noise (or synaptic input) knocks the neuron over threshold to V_{peak}, s will eventually increase until there is no stable peak threshold (e.g., 0.9), and the membrane potential will recover to rest.

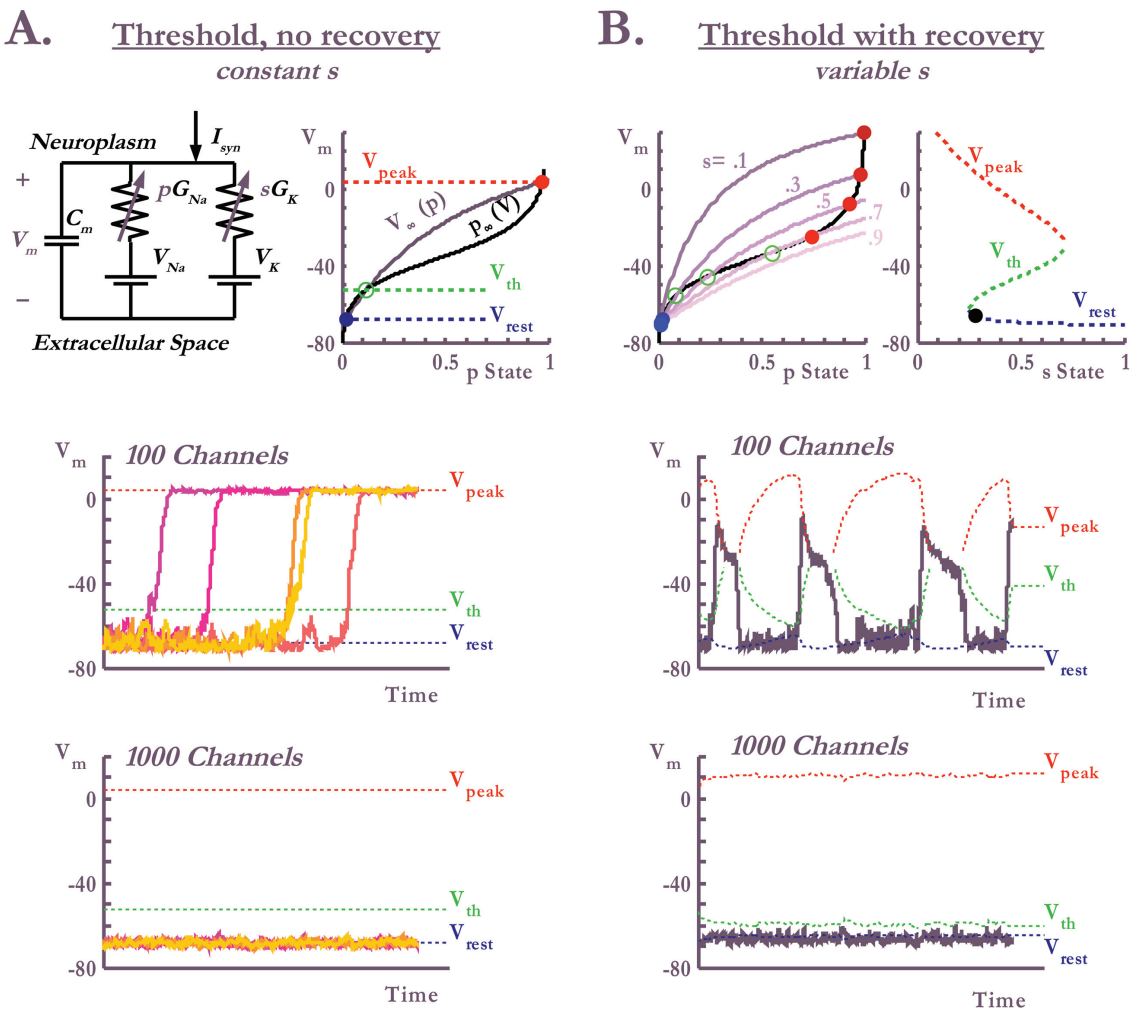

Fig. 3. Model Neuron with Na^+ channel flicker. The basic mechanisms of Na^+ channel-flicker induced rhythmic behavior. *A*, A neuronal circuit model (*top-left*), simplified from the Hodgkin-Huxley construction.* With s held constant, $V_\infty(p)$ and $p_\infty(V_m)$ are plotted on the same graph. The lines intersect at two stable fixed points (closed circles), peak potential (red) and rest (blue), and one unstable fixed point (open green circle). Membrane potential traces from five simulations in neuronal models with 100 (*middle*) and 1000 (*bottom*) Na^+ channels. In all 100-channel simulations, channel flicker eventually drives membrane potential above threshold. *B*, The same model with variable s. $p_\infty(V_m)$ is the same black line as in panel *A*. $V_\infty(p)$ is plotted for five values of s (*top-left*). As s varies, the fixed points not only change position but cease to exist as the lines separate from each other. For very high s, expected at the peak of an action potential, the pink line drops below the black line, and the V_{peak} and V_{th} fixed points disappear. The fixed points can be plotted as a function of s (*top-right*). At high s, only the V_{rest} state exists, enabling the neuron to repolarize after reaching action potential peak. At low s, only the V_{peak} state exists, enabling hyperpolarization "rebound" spikes. The black dot identifies the three-way fixed point at which V_m, s, and p are all stable. This model was simulated with 100 (*middle*) and 1000 (*bottom*) Na^+ channels. The noise in the 1000-channel case is not enough to drive the membrane potential past threshold. In contrast, noise in the 100-channel case drives V_m over V_{th}, at which point V_m quickly approaches V_{peak}. The high V_m increases s, which lowers V_{peak} and raises V_{th} until they annihilate at the *right* knee of the *upper-right* plot. With V_{rest} as the only stable fixed point, V_m returns to rest. We see from the simulation that recovery of the V_{th} fixed point governs the timing of the next event. That recovery, and hence the timing of the next event, is governed by the rate constants of s, leading to the rhythmic nature of the response.
*The HH leak conductance is incorporated into the K^+ conductance, which has a single activation variable: s = .05 + .95n, where n is the standard K^+ activation variable. All parameters were taken directly from the HH model with G_K increased to 208 mS/cm^2. In panel *A*, s is fixed at 0.4.

These relationships can be summarized by tracking the fixed points of the V_m-vs-p system in the V_m-vs-s plane (Fig. 3*B*, *top-right*). In the absence of noise, the system sits at the three-way fixed point denoted by the black circle. If noise nudges V_m above V_{th}, membrane potential shoots up to V_{peak}. Once there, s slowly increases, decreasing V_{peak}. The system moves down the red-dotted line until the right knee of the curve where V_{peak} disappears

altogether and membrane potential drops back to V_{rest}. Once at rest, s decreases along the blue-dotted line until the system reaches the three-way fixed point.

The lower two plots of Figure 3*B* each show an example membrane potential trace, with corresponding time-varying fixed points, when the number of Na^+ channels in the neuron is 100 (*top*) or 1000 (*bottom*). In the case of fewer Na^+ channels, the system oscillates. Once noise knocks the membrane potential over threshold, it quickly rises to meet the rapidly decreasing peak potential. Shortly thereafter, the peak and threshold potentials annihilate and the neuron returns to rest. Because the Na^+ channel rate constants are much faster than their K^+ channel counterparts, the time course of event initiation is governed more by the recovery of threshold (green-dotted line) than by the specific noise pattern. Hence even though the oscillations are noise-driven, they are fairly rhythmic. Although the 1000-channel neuron is capable of the same oscillations, there is not enough channel-flicker noise to push the system over threshold without some additional excitation.

Thus is described a simple, general mechanism whereby Na^+ channel-flicker may lead to oscillating neuronal behavior. The amplitude and time scale of the oscillations are critically dependent on the exact rate constants, the Nernst potentials, the maximum conductances, the number of gates per channel (simplified in this update to one), and a host of other parameters. The qualitative behavior is, however, relatively general. If a neuronal rest state is near the threshold for some activity—such as spike initiation, subthreshold oscillations, or bursting—Na^+ channel noise can theoretically push the neuron over that threshold to initiate a startling rhythmic activity. If and under what conditions Na^+ channel noise actually enables these rhythmic behaviors in living neurons are empirical questions currently addressed by many groups. Recent results are highlighted below.

Where Channel Noise Does Create a Rhythm

Channel-stochasticity effects are difficult to study experimentally because conductance means and variances cannot be disambiguated biologically. Computationally, however, models that fix conductance averages but alter the variance are trivial to construct. Using computational models, White and colleagues (1998) examined the effects of Na^+ channel stochasticity in stellate neurons of the entorhinal cortex. In response to some minor excitation, stellate neurons exhibit a prominent membrane potential oscillation between 4 and 12 Hz. In models, these subthreshold oscillations could only be generated by the channel flicker of a small subpopulation of Na^+ channels, the so-called persistent Na^+ channels (White and others 2000). More recently, others have also shown that the range of oscillation frequencies cannot be explained, or reproduced in a model, without the inclusion of channel noise (Erchova and others 2004). To test these result experimentally, however, we need a way to alter the Na^+ channel noise without changing the average Na^+ conductance.

The dynamic clamp technique enables us to combine the highly flexible computational models with living neurons to examine channel-stochasticity effects in vitro (Robinson and Kawai 1993; Sharp and others 1993). Via dynamic clamp, a computationally modeled conductance can be inserted virtually into a living neuron. If the speed of the dynamic clamp system is sufficiently faster than the time constants of the model conductance, the neuron behaves as if the model were a true population of ion channels.

In work with John White, we developed a dynamic clamp system that could run fast enough to generate Na^+ conductances in vitro (Dorval and others 2001). We used the system to test directly the role that Na^+ channel stochasticity plays in generating subthreshold membrane potential oscillations in stellate neurons (Dorval and White 2005). An illustration of our dynamic clamp technique is shown in Figure 4*A*. First, the normal persistent Na^+ conductance is removed pharmacologically by bath application of riluzole (Urbani and Belluzzi 2000). An electrode, patched into a stellate neuron, reports membrane potential V_m to a dynamic clamp computer. The computer calculates the Na^+ channel activation variable p as a function of V_m. The computer uses p to calculate the persistent Na^+ current, which it sends through the electrode into the cell.

In separate trials, we calculated p from either *ideal* or *noisy* models. In both cases, the dynamic clamp system replaced the small amount of persistent Na^+ conductance that the riluzole removed. In the ideal case, the replacement conductance was noise free: we calculated a smooth p, consistent with the Hodgkin and Huxley approach. In the noisy case, p had the appropriate variance from the small number of Na^+ channels being replaced. When neurons in either case were depolarized enough, both fired action potentials in small clusters, consistent with control data (Fig. 4*B*, *left*). Before spiking, however, only the noisy model of Na^+ conductance elicited robust subthreshold oscillations, similar to control data (Fig. 4*B*, *right*). Hence, whereas the average persistent Na^+ conductance may have other roles to play in stellate neurons, the channel flicker is directly responsible for the rhythmic subthreshold oscillations that characterize these cells.

Effects of Channel Noise

In addition to generating some rhythmic behaviors, Na^+ channel flicker modulates others. In many neurons with prominent subthreshold oscillations, action potential timing is highly dependent upon the phase of the oscillation (Desmaisons and others 1999). Furthermore, the amplitude of the subthreshold oscillation interacts with the Na^+ channel flicker to help set the precise times of action potentials superimposed on the oscillation (Dorval and White 2005). In a biophysically realistic neuron model, channel flicker elicits more variable interspike-intervals, makes the number of spikes in a burst less predictable, and blurs the transition from isolated spiking to bursting (Rowat and Elson 2004). Even when neurons are not behaving rhythmically, channel

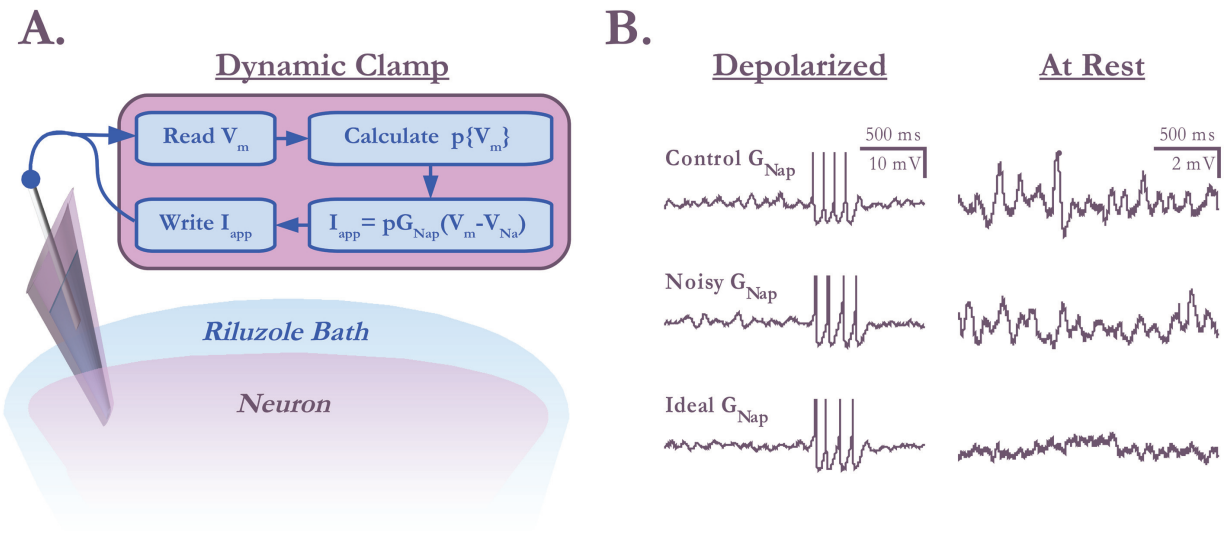

Fig. 4. Na^+ channel flicker. Dynamic clamp experiments demonstrate the dependence of a neuronal rhythm on Na^+ channel flicker (summary of work by Dorval and colleagues 2005). *A*, A schematic of the dynamic clamp technique applied to virtual replacement of a population of persistent Na^+ channels. A stellate neuron resides in a riluzole bath. An electrode samples membrane potential. The computer simulates the fraction of Na^+ channels that would be open if they were not pharmacologically blocked by riluzole. The computer calculates the current that would flow through those channels and presents it through the electrode to the neuron. *B*, In response to enough depolarizing current, the Hodgkin-Huxley style *ideal* model and a model that takes into account the *noisy* channel flicker both yield clusters of periodic action potentials, consistent with control data. Near rest, however, only the model that incorporates channel flicker reproduces the prominent subthreshold oscillations that characterize stellate neuronal responses.

noise likely contributes to spike time precision and reliability (Schneidman and others 1998).

Although we have described a mechanism that enables channel noise to drive a neuron over some threshold, channel flicker has not yet been shown to initiate periodic action potentials. The Na^+ channel population most responsible for action potential initiation numbers in the tens to hundreds of thousands in the somatic membrane: far too many for stochastic effects to be significant. In general, this may be a fortunate reality. Stochastically generated action potentials, even if they were roughly periodic, would likely interfere with the information a neuron was trying to transmit. So are there cases in which stochastically induced action potentials occur? Perhaps not in large cell bodies with tens of thousands of Na^+ channels. But the number of channels drops with the surface area of the membrane, which may constrain smaller neuronal structures.

From this insight, Faisal and colleagues (2005) showed that Na^+ channel stochasticity places hard limits on how small a neuronal axon can be. With a diameter of less than 100 nm, Na^+ channel flicker-induced rhythmic spiking would dominate axonal behavior, with tens to hundreds of spurious action potentials triggered per second. From a vast search of the anatomical literature, they provide evidence that nature did not evolve axons with diameters less than 100 nm, in agreement with their prediction. Along similar lines, Kole and colleagues (2006) recently reported potentially significant channel-flicker effects from a mixed cation channel responsible for the hyperpolarization-activated current I_h. Because these I_h channels are densely packed in small dendritic tips, their stochastic effects would greatly impact the reception and integration of synaptic inputs. Kole and colleagues argue that evolution has mitigated this problem by making individual I_h channels minimally conductive, with less than 5% of the conductance of the Na^+ channels we explored above. More channels with smaller individual conductances enable the same average conductance with much less noise.

As indicated by the I_h study, Na^+ channels are not the only source of neuronal ion channel stochasticity. In a model, Schmid and colleagues (2004) have shown that blocking (or inactivating) K^+ channels is an extremely effective way to add channel noise to a membrane, increasing the chance for stochastically generated rhythmic events. Even when K^+ channel noise is not important, K^+ channels are intimately linked to stochastic behaviors. For example, the time constants of K^+ channel deactivation may decide the rate at which rhythmic events recur, as shown by the recovery of the green-dashed threshold line in the middle graph of Figure 3*B*. Others have suggested that neurons may tune their K^+ channel time constants to exploit their effects of rhythmic behavior and spike time reliability (Schreiber and others 2004). Whether neurons down-regulate or modulate their K^+ channels to increase rhythmic events remains an open experimental question.

Finally, a word about other noise sources in neurons. In the literature, the effects of channel noise are often overshadowed by synaptic input noise in vivo. The interplay between these noise sources has not been well studied experimentally, because channel noise is too difficult to

manipulate in the living organism and synaptic noise is greatly reduced in tissue slices. Some work suggests that synaptic noise dominates the membrane potential power spectrum below 100 Hz (Jacobson and others 2005) and during transient inputs (van Rossum and others 2003). However, channel noise would be the dominant noise source amid relatively constant inputs and at high frequencies, consistent with the high rates of channel flicker.

The full extent to which channel stochasticity drives neuronal rhythmic behaviors, and their relationships to responses at the network and organism level, remains to be studied. We have provided a putative simple mechanism and shown that in at least one case, channel flicker has rhythmic consequences at the neuronal level. Hence stochastic effects must be included in the behavioral description of some neurons. As neuronal rhythms are likely to drive neural networks and behavior at the level of the organism, ion-channel flicker may still be underappreciated.

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