Chapter 24
Stochastic Ion Channel Gating and Probabilistic Computation in Dendritic Neurons

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Abstract The electrical signals underlying neural computations are mediated by membrane ion channels. Although these ion channels are well known to operate stochastically, most computational models of dendritic neurons instead make the approximation that ionic conductances are deterministic. We review the basic mathematical considerations underlying this approximation and new efficient simulation tools that allow it to be evaluated systematically. We show how this approximation breaks down for dendritic neurons, with the relative functional influence of stochastic ion channel gating likely to depend strongly on neuron type. An important consequence of stochastic gating of ion channels may be that it causes dendritic neurons to integrate synaptic inputs probabilistically, rather than in the all or nothing fashion predicted by deterministic models.

24.1 Introduction

Neural circuits are computational devices. Increasing experimental evidence indicates that key neural computations involve biochemical and electrical signals that are localized to subcellular compartments such as synapses and dendrites. In very large compartments, such as the cell soma, biochemical and electrical signaling is mediated by many thousands of molecules and is typically reliable, with fluctuations that are small relative to the signals generated. However, many neural computations take place in smaller subcellular compartments, such as dendrites, in which relatively few molecules mediate biochemical and electrical signaling. Because molecular reactions are stochastic, signaling at the subcellular level may therefore

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be unreliable. While the consequences of this stochasticity have been overlooked in many studies, recent theoretical evidence suggests that stochastic effects may fundamentally shape computation in neural circuits. Here, we will address the influence on neural computations of stochastic gating of ion channels found in dendrites. Other recent work has addressed consequences of stochastic biochemical signaling including molecular diffusion, probabilistic biochemical reactions, and stochastic gene expression (Raj and van Oudenaarden 2008; Bhalla 2004a, b).

We will address three questions. How can the impact of stochastic ion channel gating on dendritic computation be predicted? What are the effects of stochastic gating of dendritic ion channels on neuronal membrane potential dynamics? Does unreliability of signaling, particularly by stochastic dendritic ion channels, have functional consequences for computations carried out by neurons? We will first review basic principles of ion channel gating and theoretical considerations for the impact of stochastic ion channels in dendrites. We will highlight practical difficulties in simulating stochastic ion channel gating in dendrites and review new simulation tools that solve many of these difficulties. We will then show how these tools reveal influences of dendritic morphology on the functional impact of stochastic ion channel gating and how this stochastic gating leads to probabilistic modes of dendritic communication. Finally, we will suggest key areas for future research.

24.2 Stochastic Gating of Dendritic Ion Channels

Cells generate electrical signals by opening and closing of ion channels that selectively conduct specific ions. Some of these ion channels are sensitive to the membrane voltage (voltage-gated ion channels) whereas others are influenced by neurotransmitters (ligand-gated ion channels). The resting membrane potential of most neurons is determined primarily by leak potassium channels, while the rapid depolarization of an action potential is due to opening of voltage-gated sodium channels. Fast excitatory synaptic transmission typically involves opening of ligand-gated ion channels that selectively conduct sodium and potassium ions, while fast inhibitory transmission is typically through ligand-gated ion channels that selectively conduct chloride ions. In almost all models of electrical signaling in neurons the properties of single ion channels are not accounted for. Instead, electrical signals are modeled as arising from macroscopic conductances that represent the collective behavior of large populations of ion channels (Hodgkin and Huxley 1952; Hines and Carnevale 1997). In these models, conductances change smoothly over time and react deterministically to the model's voltage dynamics, while ion channels are assumed to be continuously distributed in the cell membrane rather than localized to particular points in space.

These assumptions are in contrast to data from patch-clamp recordings which show that macroscopic conductances are mediated through opening and closing of many single ion channels (Neher and Sakmann 1976). If the behavior of a single ion channel is recorded in stationary conditions, its conductance is not constant, but

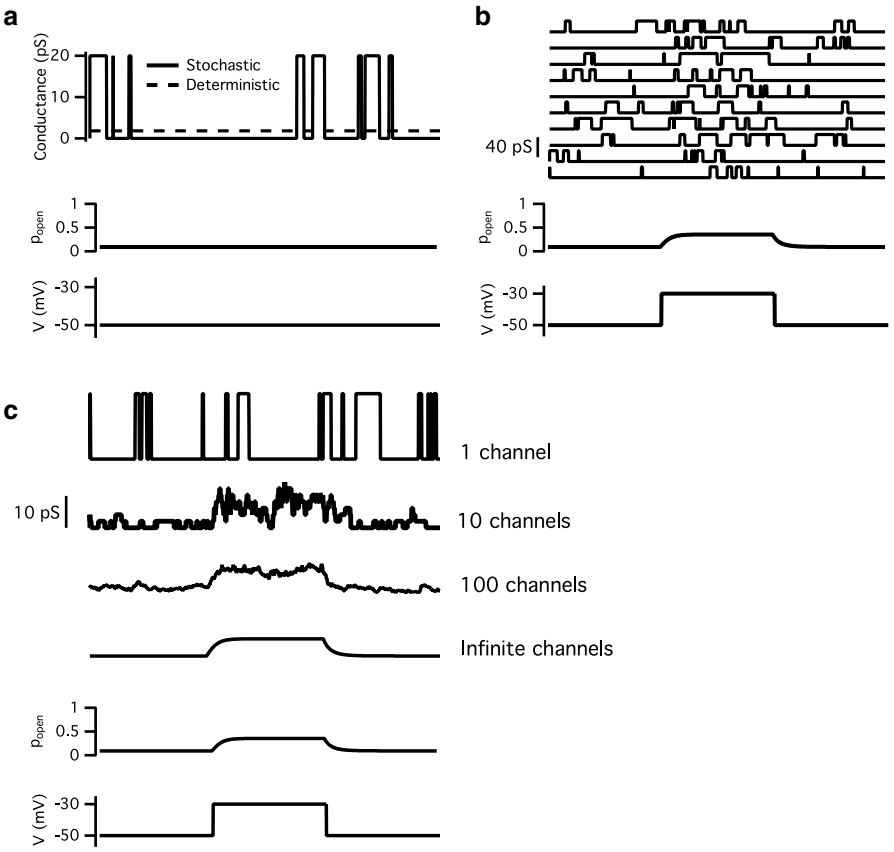

Fig. 24.1 Examples of fluctuating currents from simulated Hodgkin–Huxley potassium channels. (**a**) A single channel shows a fluctuating conductance (*top*, *solid trace*) by opening and closing randomly even when subject to a stationary voltage (*bottom*) at a fixed open channel probability (*middle*). The equivalent deterministic conductance is also plotted (*top*, *dashed trace*). (**b**) The channel responds to a depolarizing voltage step (*bottom*) with an elevated open probability (*middle*). Notably, the conductance response (*top*) is different on each trial (*sequential rows*) despite an identical stimulus. (**c**) The conductance response (*top four traces*) to a voltage stimulus (*bottom trace*) is less noisy for larger ion channel populations. For this illustration, single channel conductances were scaled inversely to channel number in order to normalize total conductance amplitudes

instead jumps rapidly between discrete closed and open states (Fig. 24.1a). Typically the open states of single ion channels have conductances from <1 pS to as high as 150 pS (Hille 2001). Stimuli that modulate macroscopic ionic conductances usually do so not by modulating the single channel conductance, but by influencing the probability that single channels will be in their open state. For example, changes in membrane potential influence voltage-gated ion channels by modulating the probability of their opening. As a result, a single ion channel generates unpredictable

step-like responses to a repeated stimulus (Fig. 24.1b). In contrast, the responses of large populations of ion channels are predictable and show relatively little trial-to-trial variability (Fig. 24.1c). A key question then is to what extent the variability arising from stochastic ion channel gating influences neuronal function and to what extent it should be included in models of neuronal signaling. Before addressing this question we consider the properties of single ion channels found in dendrites of central neurons.

Cell-attached patch-clamp recordings and antibody labeling data demonstrate localization of voltage-gated ion channels to dendrites of many neuron types (Spruston 2008; Magee 2000; Johnston et al. 2003; Reyes 2001; Nusser 2009). The estimated densities of channels in dendritic membrane range from fewer than 1 μm^{-2} to greater than 500 μm^{-2} (Kole et al. 2006; Engel and Jonas 2005; Chen and Johnston 2004). In cortical pyramidal neurons dendritically located voltage-gated Na^+ and K^+ channels support propagation of action potentials in anterograde and retrograde directions in the dendritic tree. Hyperpolarization-activated cation channels (HCN channels), which mediate the hyperpolarization-activated current I_h, and some other K^+ channel types, for example mediating the A current, have little influence on action potential propagation, but instead influence integration of synaptic responses (Robinson and Siegelbaum 2003; Magee 2000; Wahl-Schott and Biel 2009; Johnston and Narayanan 2008). Most electrophysiological investigations of dendritic ion channels have relied on macroscopic currents that reflect gating of many ion channels within the patch of recorded membrane (Hoffman et al. 1997; Johnston et al. 2003), but single channel recordings from dendrites have been reported in a few studies (Chen and Johnston 2004; Magistretti et al. 1999; Magee and Johnston 1995; Bittner et al. 2012). These studies reveal the kinetics of dendritic ion channel gating and show that macroscopic dendritic conductances can be explained by changes in single channel open probability. Typical single channel conductances of dendritic voltage-gated Na^+ and K^+ channels are 15–30 pS (Chen and Johnston 2004; Magee and Johnston 1995). In contrast, the single channel openings of dendritic HCN channels have not been observed directly, but have been inferred from noise analysis to be less than 1 pS (Kole et al. 2006). The reasons for this diversity of single channel conductances are not yet clear, but a possibility raised by the work we describe below is that it enables fine tuning of the functional consequences of stochastic ion channel gating.

24.3 Theoretical Considerations for Impact of Stochastic Dendritic Ion Channels

Are deterministic models sufficient to explain dendritic computation? Or are there circumstances in which it is necessary also to take account of stochastic gating of single channels? We first address these questions by examining a simple model. Consider a population of N stochastically gating ion channels in a cell membrane,

each with the same open probability p and single channel current i. The mean current through this population of channels is:

$$I = iNp$$

In a deterministic model the current flowing through these channels is always equal to the mean current. In contrast, for real populations of channels, and for models that account for their stochastic opening and closing, the actual population current fluctuates around the mean value, hence generating electrical *noise* around the mean *signal*. The standard deviation of these current fluctuations is a natural measure of the amplitude of this noise, and is given from binomial statistics as:

$$\sigma = i\sqrt{Np(1-p)}.$$

This equation leads to a number of predictions. First, the absolute amplitude of noise is maximal when $p=0.5$, and minimal when $p=0$ or $p=1$. Below action potential threshold, most ion channels in the nervous system have open probabilities less than 0.5. In this range, increasing the open probability will increase the current fluctuations. Because for many ion channels p increases upon depolarization (Hille 2001), this suggests that the absolute amplitude of ion channel noise will increase with depolarization. In contrast to the absolute amplitude, the relative amplitude of fluctuations, when defined as the standard deviation of the current divided by its mean, is proportional to $\sqrt{\frac{(1-p)}{p}}$. Because this quantity decreases with increasing p, the *relative* amplitude of fluctuations usually decreases upon depolarization. Second, because the standard deviation is proportional to $\sqrt{N}$, the absolute amplitude of current fluctuations will be greater for larger populations of ion channels. On the other hand, because the mean current is proportional to N, the relative amplitude of current fluctuations will decrease for larger populations of ion channels. Third, larger single channel currents will also lead to greater amplitude current fluctuations (both absolutely and relatively). Because single channel currents can differ by three or more orders of magnitude between channel types, both because of differences in single-channel conductances and differences in reversal potentials (Hille 2001), this could lead to considerable diversity in the impact of stochastic ion channel gating.

How will current fluctuations from the ion channel populations influence membrane potential dynamics? When current flows through an ion channel it can modify the membrane potential by charging or discharging the membrane capacitance or it can flow axially to other parts of the cell (Rall 1959, 1962). The functional impact of stochastic ion channel gating therefore depends not only on the properties of stochastic currents, but also on the electrical properties of the cell in which they take place. The cell membrane's parallel capacitance and resistance act as a low-pass filter—they preferentially attenuate high frequency components of membrane currents. The product of the capacitance and resistance determines the time constant of filtering, while the resistance sets the amplitude of membrane potential changes. The low pass filter characteristics of the membrane suggest that current fluctuations

from ion channels with faster gating kinetics will be more attenuated than those from channels with slower gating kinetics (DeFelice 1981). This prediction is confirmed by simulations comparing channels with different physiological gating kinetics (Cannon et al. 2010). In addition to membrane properties, the cytoplasmic resistivity will influence the axial flow of ionic currents. Because axial flow of current is determined by axial resistance, membrane resistance and membrane capacitance throughout a cell, the cell's morphology and the spatial arrangement of the cell's compartments influences both the local and distal impact of stochastic current fluctuations. Finally, the cell's eventual voltage dynamics will also depend on its entire complement of ion channels, and on the cell's level of depolarization. For example, in most cells near resting potential small voltage transients are dampened and quickly decay back to rest. In contrast, at membrane potentials nearer to spike threshold the voltage dynamics become nonlinear. In this region, small voltage fluctuations from channel noise can be quickly amplified by the macroscopic dynamics, leading to large amplitude transients or oscillations (White et al. 1995, 1998). If the fluctuations are large enough, they may even trigger action potentials (Skaugen and Walloe 1979; Johansson and Arhem 1994). Hence, microscopic fluctuations from stochastic channel gating can have large macroscopic consequences (Schneidman et al. 1998; Dudman and Nolan 2009; Faisal et al. 2005). This sensitivity to noise near threshold reflects a general property of all nonlinear excitable systems near a bifurcation (Lindner et al. 2004).

In summary, a number of factors may determine the influence of stochastic ion channel gating on neuronal computation. Together, single channel conductance, the number of channels and their open probability determine the amplitude of current fluctuations that arise from a population of channels. The impact of these current fluctuations on membrane potential dynamics is determined by local membrane capacitance, axial current flow, and presence of other ion channels. This suggests that in principle stochastic ion channel gating could profoundly influence membrane potential dynamics, particularly in small electrically isolated structures. However, because many of the properties that will determine the influence of stochastic ion channel gating vary both within and between cells, predicting the functional consequences of stochastic ion channel gating requires models that account for these details in a particular neuron.

24.4 Simulation of Stochastic Ion Channels in Complex Neuronal Morphologies

The computational demands of accurately simulating model neurons in which all ion channels gate stochastically have until recently made it impractical to carry out detailed investigations of the consequences of stochastic ion channel gating. The scale of this challenge is illustrated by the fact that a single neuron has on the order of one million ion channels, each at a different location on its membrane, and because each channel gates independently and stochastically, any channel might

switch state at any moment in time. There are two different general approaches to this problem. Microscopic models describe individual ion channels as continuous-time Markov chains where stochastic transitions occur between discrete states. In contrast, stochastic differential equation (SDE) models describe ionic currents as the sum of a deterministic Hodgkin–Huxley-style component plus a stochastic noise component.

24.4.1 Microscopic Models of Ion Channel Gating

In microscopic descriptions each ion channel is considered a distinct object which can exist in one of several discrete states. These states typically correspond to different conformations of the ion channel protein. At least one of the states is "open" (the channel passes current), and at least one state is "closed" (the channel does not pass current). The channel is considered memoryless (the Markov property), so that the length of time the channel has spent in the present state has no bearing on its future behavior. Transitions between states are driven by thermal fluctuations, and because actual transition times are on the order of nanoseconds (Hille 2001), for modeling purposes they are usually assumed to be instantaneous. For voltage-gated ion channels, the membrane voltage influences the probability of transitions between states. For example, a Na^+ channel will be more likely to switch to an open state upon depolarization. Most microscopic simulation methods use Monte Carlo techniques. The most conceptually simple way to do this is to first, after choosing a small time step Δt, convert each transition rate, k, in a channel's kinetic scheme to a transition probability, p by assuming $p \approx k\Delta t$. Then, for each time step, a random number x between zero and one is drawn for each channel. If $x < p$, the state transition is performed. However, for realistic neuronal simulations this approach is prohibitively expensive because it requires the generation of at least one random number for each ion channel at each time step. For example, if a neuron model containing one million two-state ion channels were to be simulated with a time step of 1 μs, then one millisecond of simulation time would require generation of $10^6 \times \frac{1ms}{1\mu s} = 10^9$ random numbers, each to be compared to transition probabilities, in addition to the normal calculation of the voltage dynamics.

A solution to this problem comes from algorithms developed to accelerate simulation of stochastic chemical reactions (Gillespie 1977, 2001; Cao et al. 2006). In early algorithms, following each channel transition random numbers are drawn to determine both when the next transition will occur, and which transition will occur (Skaugen and Walloe 1979; Chow and White 1996). Then the simulation steps forward in time by the calculated interval and performs the corresponding state transition. Although this algorithm is exact, meaning that it has zero approximation errors, it does not scale well to many ion channels. More recently, we developed software called the Parallel Stochastic Ion Channel Simulator (PSICS) to enable

more efficient simulation of stochastic ion channel gating in spatially distributed neuron models (Cannon et al. 2010). This simulator, which is used for the studies described in detail here, includes several approaches to speed up simulations without compromising accuracy:

1. It groups together the ion channels in each state per spatial compartment, enabling stochastic calculation of the *numbers* of channels making a certain transition instead of performing the calculation for each channel independently. This grouping is allowable because sufficiently nearby ion channels can be considered interchangeable from an electrical point of view. That is, they are subject to and influence the same local membrane potential.
2. It uses a version of the tau-leap method (Cao et al. 2006), where multiple state-transitions are allowed within a single time step, even for a single ion channel. This allows for longer time steps and hence faster simulation. However, the changes at the end of the time step must be evaluated to make sure that voltage would not have changed so much during the time step that the assumption of fixed transition probabilities was unjustifiable.
3. It ignores state transitions that are highly improbable, according to a specified threshold.
4. It precomputes lookup tables for the state-transition probabilities over the anticipated voltage range.

When these approaches are combined, simulation of detailed and realistic compartmental models of neurons becomes possible in a reasonable period of time (Cannon et al. 2010).

24.4.2 Stochastic Differential Equation Models of Ion Channel Gating

The SDE approach for simulating ion channels was pioneered with the hope of providing faster simulation algorithms than the Monte Carlo techniques (Fox and Lu 1994; Fox 1997). In early descriptions, the membrane conductance gating variable dynamics were reduced to a Langevin equation:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \alpha\left(1-x\right) - \beta x + \eta\left(V, t\right)$$

where x is a given Hodgkin–Huxley gating variable, α and β are voltage-dependent transition rates, and $\eta(V, t)$ is a zero-mean Gaussian noise term. Note that this is equivalent to the classic Hodgkin–Huxley description plus a stochastic noise term.

Although relatively fast to compute, in this form the algorithm shows poor approximation to the exact solutions, even in the limit of a large population of ion channels (Mino et al. 2002; Bruce 2009). This is because it does not accurately capture correlations in fluctuations between channel states (Bruce 2009; Goldwyn

et al. 2011; Linaro et al. 2011). In general, the difficulties in the SDE approach arise in deciding where to insert the noise term (as a current, conductance, or channel subunit fluctuation), deciding how the noise intensity should scale as voltage changes, and deciding how to accurately account for temporal correlations in the noise. The primary discrepancies have only recently been resolved by modeling the noise statistics based on single channel properties rather than on channel subunit properties as in earlier studies (Goldwyn and Shea-Brown 2011). Despite these advances, further approximations in the SDE approach await resolution: for example, at present the noise statistics may lag the voltage dynamics during fast transients (Linaro et al. 2011). In addition, the relative speeds and approximation errors of modern SDE approaches versus modern Markov-chain simulation algorithms (Cannon et al. 2010) remain unquantified, making it unclear which approach is best for a given simulation problem. Indeed, SDE approaches are yet to be applied successfully to investigation of stochastic ion channel gating in dendrites.

24.5 Dendritic Morphology Determines the Influence of Stochastic Ion Channel Gating

Does stochastic gating of ion channels influence membrane potential dynamics in dendrites and what is the impact of dendrite morphology on the functional consequences of stochastic ion channel gating? Previous simulations suggest that stochastic ion channel gating causes larger fluctuations in the membrane potential of dendritic neurons compared to spherical neurons of a similar surface area (van Rossum et al. 2003), but these simulations did not evaluate different dendritic structures or distinct neuron types. By developing software for efficient simulation of stochastic gating of ion channels in spatially extended model neurons, we have been able to address these issues directly (Cannon et al. 2010). To do so, we compared membrane potential activity of 29 reconstructed neurons corresponding to six different neuron types. To isolate the influence of neuronal morphology we inserted the same density of ion channels in the membrane of each simulated neuron. Ion channel models and distributions were implemented according to a previously published neocortical pyramidal neuron model (Mainen and Sejnowski 1996). The leak conductance was modeled as a mixture of voltage-independent Na^+ and K^+ channels with open probabilities of 0.7 and density of 0.016 μm^{-2}. Active channels included fast Na^+ channels (1 μm^{-2}), non-inactivating K^+ channels (0.05 μm^{-2}), and high-voltage Ca^{2+} channels (0.15 μm^{-2}). Because ion channels distributions were identical across neurons, differences in voltage fluctuations must reflect differences in morphology.

We found that with these parameters stochastic ion channel gating caused the resting membrane potential of all simulated neurons to fluctuate with standard deviation up to 0.8 mV. This is in agreement with experimental measurement of voltage noise from cultured neurons (Diba et al. 2004) and from neurons in brain

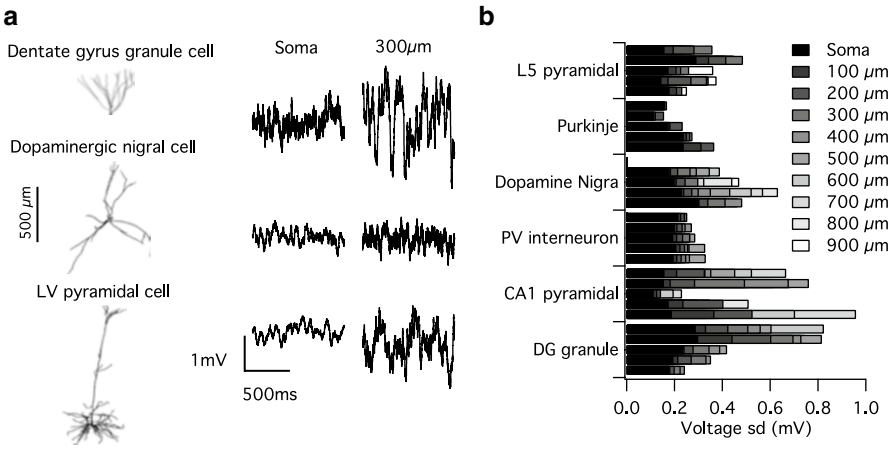

Fig. 24.2 The impact of stochastic ion channel gating depends on neuronal morphology. (**a**) Example resting membrane potential traces (*right*) from three model neurons with dendritic arbours from different cell types (*left*). Traces are from soma and at a dendritic location 300 μm from soma. (**b**) Standard deviation of the resting voltage for 29 reconstructed neurons from six different cell types. Greyscale level indicates dendritic distance from soma. Note that the amplitude of fluctuations depends on cell type, and is generally larger in the dendrites than at the soma. Adapted from Cannon et al. (2010)

slices (Jacobson et al. 2005). Comparison of voltage fluctuations at different locations along the dendrites of the simulated neurons reveals that the amplitude of the fluctuations increases with distance from the soma (Fig. 24.2). Thus, stochastic gating of ion channels can contribute to the voltage noise in neurons and this noise is greatest in more distal dendrites. When we compared voltage fluctuations between different neuron types we found striking differences. For example, noise from stochastic ion channel gating was relatively small in simulated Purkinje cells and parvalbumin positive interneurons, but was much larger in CA1 pyramidal neurons (Fig. 24.2). This suggests that the impact of stochastic gating is sensitive to differences in morphology that are found between different neuron types. These effects are likely mediated both by differences in the degree of axial charge flow and differences in local membrane impedance profiles across neural morphologies (as discussed earlier). Both of these properties are influenced by dendritic diameter, length and branching pattern (Koch 1999).

To test the effects of channel kinetics on voltage noise we reduced the time constants for the gating of leak channels tenfold. This manipulation changes only the rate of switching between open and closed states while leaving the mean fraction of open channels unaltered. This change caused the amplitude of the voltage fluctuations to increase approximately threefold, but dependence of noise on dendritic location and differences between neuron types were maintained, indicating that in realistic neuronal morphologies channel kinetics will influence the amplitude of voltage fluctuations resulting from stochastic ion channel gating (Cannon et al. 2010).

Together these simulations demonstrate that neuronal geometry critically determines the influence of stochastic gating on membrane potential dynamics. They also show that geometry and ion channel properties interact, with slow gating ion channels causing larger membrane potential fluctuations. While these results demonstrate that models which include physiologically realistic ion channel and membrane properties lead to consistent functional effects of stochastic ion channel gating, the sensitivity of these effects to differences in morphology and channel properties suggests that predictions for specific cell types should be treated with care. In particular, these results indicate the importance of obtaining accurate reconstructions of neuronal morphology and more data about the single channel properties of neuronal ion channels.

24.6 Stochastic Dendrites Integrate Probabilistically

How might stochastic gating of ion channels influence neuronal computations? To address this question, it is important to establish the effects of stochastic channel gating on transformation of synaptic input into an action potential output. We therefore adopted a detailed model of a hippocampal CA1 pyramidal neuron that is well constrained by experimental data, but has previously only been simulated using deterministic ion channels (Jarsky et al. 2005). We implemented the model in a fully stochastic configuration and further refined it by adding a realistic distribution of HCN channels, which mediate the hyperpolarization activated current (I_h) (Cannon et al. 2010). These channels are expressed in an increasing gradient from soma to distal dendrites (Magee 1998; Golding et al. 2005; Lorincz et al. 2002; Nolan et al. 2004). We then investigated the response of the model to activation of 1,503 excitatory synaptic inputs located randomly throughout the basal and apical dendrites. The activity of each input followed a Poisson process and the amplitude of the inputs was adjusted so that the firing rate of the stochastic neuron was approximately 20 Hz. We chose these parameters to mimic activity levels that might occur during active theta states in the hippocampus. We reasoned that if stochastic gating of ion channels influences neuronal computation then switching the model between stochastic and deterministic configurations should modify its transformation of synaptic input into spike output.

When we compare responses to repeated presentation of the same pattern of synaptic inputs, we find as expected that the deterministic version of the model produces identical responses on each trial. In contrast, the version of the model in which all ion channels gate stochastically generates responses that differ from trial to trial (Cannon et al. 2010). In general action potentials occur at similar times in each trial, but unlike the deterministic model where the probability of spiking at a particular time point is either one or zero, in the stochastic model the probability of spiking at any time point varies between one and zero (Fig. 24.3). At times when spikes are triggered in the deterministic model they are “dropped” on a fraction of trials by the stochastic model, whereas at other times at which spikes are absent in

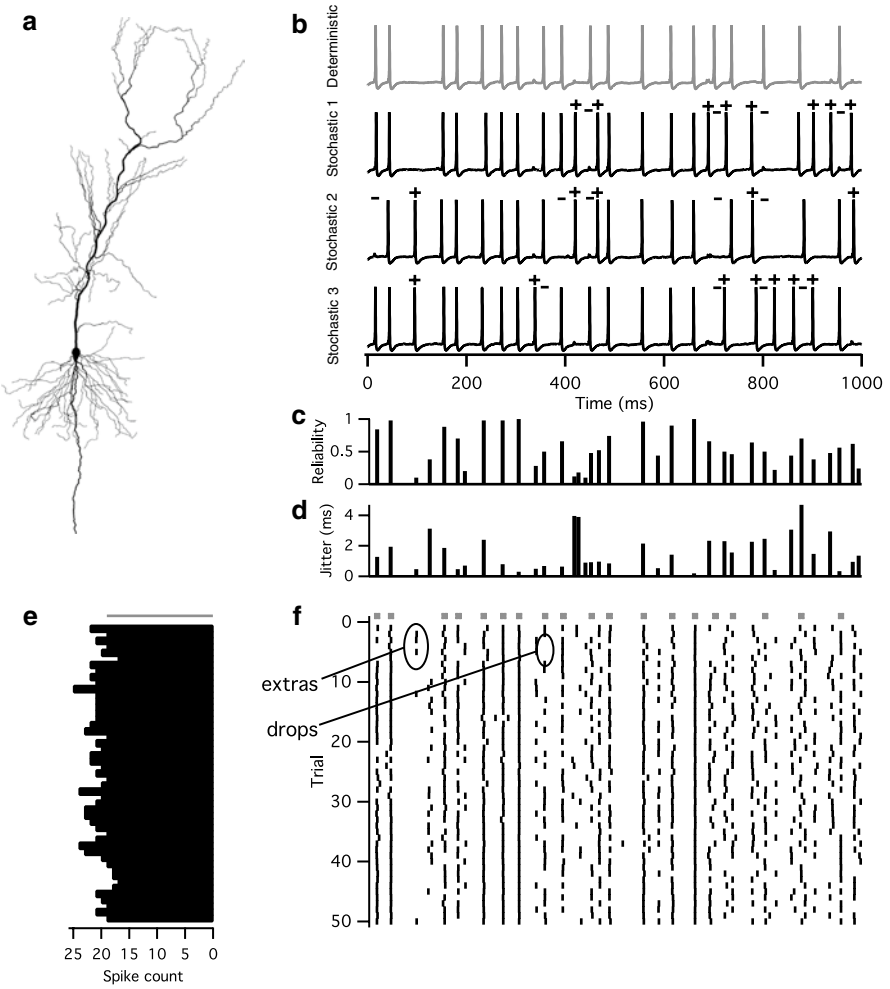

Fig. 24.3 Channel noise affects synaptic integration in a morphologically realistic neuron. (**a**) Morphology of the CA1 neuron model. (**b**) Example voltage traces from deterministic model (*grey*), and stochastic trials 1, 2, and 3 (*black*). *Plus symbols* mark "dropped" spikes and *minus symbols* mark "extra" spikes occurring on stochastic trials when compared to the deterministic trial. (**c**–**d**) Reliability (**c**), jitter (**d**) for each spike event. (**e**) Spike count for each trial in (**f**). (**f**) Raster plot of action potential times recorded at soma during 1 s of model time. One deterministic trial in *grey squares* and 50 stochastic trials in *black ticks*. Adapted from Cannon et al. (2010)

the deterministic model "extra" spikes occur in the stochastic model. We quantified the reliability of each spike as the fraction of trials on which it occurred (Fig. 24.3c). Stochastic ion channel gating also introduces considerable jitter into the timing of action potentials, quantified as the standard deviation of the spike timing (Fig. 24.3d). Whereas we find that the probability of spike initiation is modified when ion channels gate stochastically, the waveform of action potentials does not differ.

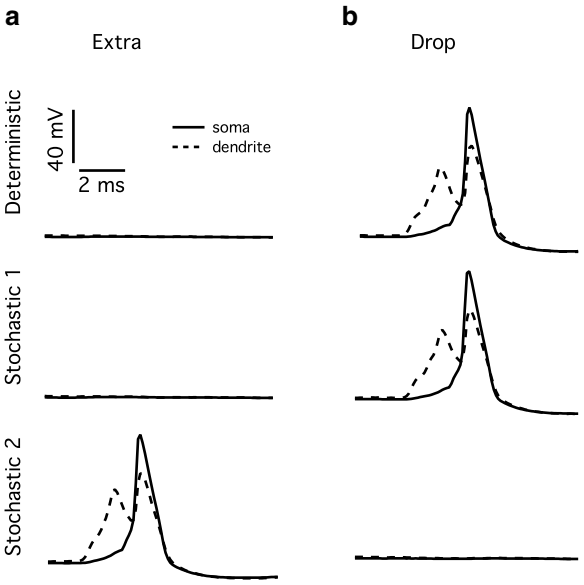

Fig. 24.4 Probabilistic dendritic events underlie probabilistic axonal firing from stochastic ion channel gating. *Rows* are example voltage traces from deterministic (*top*), stochastic trial 1 (*middle*), and stochastic trial 2 (*bottom*) simulations from Fig. 24.3. Extra (**a**) and dropped (**b**) axonal action potentials from probabilistic dendritic spikes. Adapted from Cannon et al. (2010)

This is in agreement with previous simulations of the responses of stochastic neurons which used injected current rather than distributed synaptic input to initiate action potentials (Diba et al. 2006). Together, these data predict that in real neurons, stochastic ion channel gating will cause responses to a given synaptic input to be probabilistic. This is in contrast to deterministic simulations which generate identical all-or-nothing responses to repeated presentation of the same input.

Where in the neuron does the variability in spiking originate from and do different types of ion channel, or ion channels found at different locations, preferentially contribute to the functional effects of stochastic ion channel gating? By recording the membrane potential simultaneously in each primary dendrite of the model neuron (~20 μm from the soma), the origin of the "extra" and "dropped" spikes can be addressed. This reveals that both "extra" and "dropped" somatic spikes are preceded by all-or-nothing dendritic depolarizations indicating that they originate from dendritic spikes that propagate towards the soma (Fig. 24.4).

To address the roles of particular ion channels we simulated models in which subsets of ion channels gate stochastically while the remaining ion channels gate deterministically. We found that stochastic gating of any single ion channel type causes "dropped" and "extra" spikes, but no single ion channel type alone could fully account for all of the "dropped" and "extra" spikes in the fully stochastic model. Stochastic gating of either Na^+ channels, A-type or delayed rectifier potassium channels alone caused more than 50 % of the number of "dropped" and "extra" spikes in the fully stochastic model, indicating strong redundancy in the contribution of particular ion channel types to probabilistic integration of synaptic inputs. When only axonal channels gated stochastically then the number of "dropped" and "extra" spikes was reduced by approximately 50 %, whereas when only dendritic

ion channels gated stochastically the number of "dropped" and "extra" spikes was similar to in the fully stochastic model, indicating that stochastic gating of dendritic ion channels is particularly important for probabilistic integration of distributed synaptic inputs.

Together, these data suggest that stochastic gating of dendritic ion channels may have profound effects on single neuron computations. In contrast to deterministic models where the same synaptic inputs produce the same output, when ion channels gate stochastically then the response to synaptic inputs is probabilistic. The considerable redundancy revealed by substantial numbers of "extra" and "dropped" spikes when only a single channel type gates stochastically, suggests that the basic results are robust to the exact choice of parameters. Indeed, because our choice of simulation parameters is quite conservative, it is perhaps more likely that in real neurons, ion channels with a greater conductance would further increase the impact of stochastic gating.

24.7 Other Sources of Electrical Noise in Neurons

Before discussing further functional implications of these results, it is worth considering the likely influence of noise from stochastic ion channel gating relative to that of other potential neuronal sources of noise. In general these other noise sources can be divided into two categories: synaptic and non-synaptic. Non-synaptic sources of noise include thermal or "Johnson" noise, and ion channel shot noise. Johnson noise arises from thermal fluctuations in the potential difference across a conductor (e.g., the cell membrane) and is calculated to be negligible for neural membranes (Lecar and Nossal 1971; Manwani and Koch 1999). Ion channel shot noise is generated by momentary fluctuations in the flow of discrete ions, but the high rate of ion flow in physiological currents (~10^6/s) implies that shot noise is likely negligible. Thus stochastic channel gating should be considered the dominant non-synaptic source of electrical noise. Synaptic sources of variability are numerous and include probabilistic presynaptic release of neurotransmitter vesicles, heterogeneous location of vesicle release within synapses, heterogeneity in the size of vesicles, diffusion of the neurotransmitter, stochastic binding of neurotransmitter to postsynaptic receptors, and stochastic gating of ionotropic receptors. These factors may lead to substantial variability in synaptic currents (Franks et al. 2003; Lisman et al. 2007; Faisal et al. 2008) and it will be important to establish their influence relative to that of stochastic ion channel gating.

24.8 Summary and Future Directions

Given that the functional consequences of stochastic ion channel gating are difficult to predict, but might in principle affect neuronal computation, why have they not received more attention? The success and adaptability of the original

Hodgkin–Huxley formalism for describing membrane conductances compared with the relative scarcity of studies demonstrating physiologically relevant implications of stochastic ion channel gating has justified use of deterministic approaches to understanding neuronal computations. However, the neuronal compartments where stochastic effects are likely to be greatest, such as dendritic branches, spines, and synaptic terminals, are also the least accessible to experimental analysis. Hence this confidence in deterministic frameworks may turn out not to be supported by the data. Of equal importance, the computational demands of simulating neurons with fully stochastic ion channel models have until recently made it impractical to carry out detailed simulations of morphologically realistic models of neurons in which all channels gate stochastically.

Further functional consequences of stochastic channel gating in dendrites may remain to be discovered. Questions for future research include:

- What are the implications of channel noise for neural coding? Several theoretical studies have now shown that stochastic ion channel gating can induce unreliability in neural responses, and imprecision in response timing (Schneidman et al. 1998; Dudman and Nolan 2009; Cannon et al. 2010). If information is encoded in the timing of spike sequences, then stochastic channel gating might set an upper limit on the information rate because spike timing cannot be more precise than the inherent jitter. If information were instead encoded in spike rates, then channel gating might also limit information coding by adding noise to any spike count over a short time interval (Fig. 24.3e). Alternatively, the probabilistic synaptic integration caused by stochastic channel gating may be used by the nervous system in some beneficial way. For example, one possibility is that channel noise is used to implement a "sampling" process where fluctuations in a neuron's firing pattern reflect uncertainty in the brain's inferences about the external world (Fiser et al. 2010; Buesing et al. 2011).
- How big an impact do the fluctuations from stochastic channel gating have relative to the contributions from other sources of electrical noise? For example, it is possible that probabilistic vesicle release will prove at least as significant. The answer to this question may strongly depend on cell type specific factors such as ion channel composition, dendritic morphology, and synaptic properties.
- Where in the cell does stochastic ion channel gating have the greatest impact? Our simulation results suggest that stochastic ion channel gating is of particular importance for dendritic computations. This is consistent with general biophysical considerations which suggest that voltage noise from channel fluctuations will be largest when channel numbers are small and the local membrane impedance is large. Indeed we expect that channel noise will have greatest impact in small protrusions such as dendritic spines, which to our knowledge have not yet been considered in fully stochastic simulations.
- Does stochastic channel gating introduce unreliability into intracellular biochemical signaling? Several voltage-gated ion channels, particularly those with a high permeability to calcium, serve dual roles as mediators of electrical and biochemical signaling. Because these ion channels gate stochastically, downstream sensors of these signals must also be activated stochastically, unless they

act to integrate the biochemical signals over a slower timescale to average out stochastic fluctuations. In particular, local Ca^{2+} microdomain signaling may be drastically affected by stochastic channel gating because Ca^{2+} microdomains are believed to require a few hundred microseconds to reach their steady-state concentration (Neher 1998)—a timescale comparable to the switching times of many dendritic ion channels (Magee and Johnston 1995).

In conclusion the ability to simulate stochastic ion channels distributed through neurons with arbitrary morphology has enabled direct comparison between realistic models of synaptic integration. The results indicate that in principle stochastic gating of ion channels has profound effects on neuronal computation, converting neurons from all-or-nothing to probabilistic integrators of synaptic input. Key challenges for the future are to establish the range of neuronal computations that are influenced by stochastic ion channel gating and to determine the consequences for higher level models of neuronal computation. Addressing these challenges will require more detailed and accurate experimental data and further improvements in simulation methods to enable efficient stochastic simulation of whole neuronal circuits. A final challenge is to develop experimental tests that enable simulation-based predictions of the consequences of stochastic ion channel gating to be tested in experimental models (Dorval and White 2005).

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