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Channel noise in neurons

John A. White, Jay T. Rubinstein and Alan R. Kay

The probabilistic gating of voltage-dependent ion channels is a source of electrical 'channel noise' in neurons. This noise has long been implicated in limiting the reliability (repeatability) of neuronal responses to repeated presentations of identical stimuli. More recently, it has been shown to increase the range of spiking behaviors exhibited in some neural populations. Channel numbers are tied to metabolic efficiency and the stability of resting potential, and channel noise might be exploited by future cochlear implants in order to improve the temporal representation of sound.

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WHAT FACTORS limit the reliability of neuronal responses to a given stimulus, and to what degree? The answers to these questions are of fundamental importance in neurobiology, because the reliability of neurons will constrain the nature of the computational mechanisms available to the brain[1–6]. The discussion in this article is confined to a particular aspect of this complex set of issues that can be addressed biophysically: what impact does 'channel noise', which is generated by the random gating of voltage-gated ion channels, have on the reliability and dynamics of single neurons? Evidence will be discussed in support of the hypothesis that channel noise has measurable effects under normal conditions. Novel ways to magnify the effects of channel noise for clinical gain will be reviewed, as will the potential impact of channel noise on the cellular metabolic 'economy'. The role(s) of noise from other sources (for example, synaptic processes – see Box 1) will not be covered in detail. This decision was made not to deny the importance of synaptic noise, which is certainly a major source of neuronal variability, but rather in recognition of the fact that the precise impact of synaptic noise can be evaluated only once channel noise is understood and quantified. The need for a precise, mechanistic understanding in this endeavor is particularly acute because both channel and synaptic noise sources exhibit voltage dependence, which makes their interactions difficult to understand intuitively.

Quantifying channel noise

It has been suspected since the time of Hodgkin and Huxley, and known with certainty since the landmark single-channel recordings of Neher, Sakmann and colleagues, that voltage-gated ion channels are stochastic devices. Typically, these noisy molecular devices are modeled using chemical-reaction schemes with a limited number of states and rate constants that depend on voltage alone[7]. Other modeling approaches allow rate constants to depend on both voltage and the amount of time each channel has spent in a given state[8].

Regardless of which model structure best captures the essence of voltage-gated channels, it is clear that their probabilistic gating adds noise to the total membrane current in the cell. For traditional descriptions of ion channels, the current generated by a homogeneous population of ion channels is readily quantifiable under voltage-clamp conditions[7,9]. Under steady-state voltage clamp, the population current has mean $\bar{I}$ and variance σ_I^2 given by the equations:

$$\bar{I} = \gamma N p(V)\,(V - V_{rev}) \quad (1)$$

$$\sigma_I^2 = \gamma^2 N p(V)\,[1 - p(V)]\,[V - V_{rev}] \quad (2)$$

where γ is open-channel conductance, N is the number of channels, V is membrane potential, $p(V)$ is the (steady-state) voltage-dependent probability that each channel is open, and V_{rev} is the reversal potential. A useful parameter for quantifying the noisiness of current generated by a population of channels is the coefficient of variation (CV), the ratio of standard deviation to mean:

$$CV = \frac{\sigma_I}{\bar{I}} = \sqrt{\frac{1 - p(V)}{N p(V)}} \quad (3)$$

Equation 3 implies that the noisiness of a membrane current declines in proportion to the square root of the number of channels.

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Box 1. Sources of electrical noise in neurons

The biophysical mechanisms underlying both electrical excitability and synaptic transmission in neurons are noisy: responses to repeated stimuli differ randomly from trial to trial, even in the absence of adaptation or short-term synaptic plasticity. In the case of electrical excitability, the primary source of inter-trial variance comes from the fact that individual ion channels open and close randomly. The term 'channel noise' is used in this article to denote how particular responses of populations of ion channels differ from the mean behavior, which can be quantified by examining multiple recordings in response to the same voltage-clamp stimulus. Figure Ia shows modeled voltage-clamp responses of a population of 1800 noisy Hodgkin–Huxley K^+ channels[a,b] (single-channel conductance = 20 pS; $V_m = -40$ mV; $T = 6$°C). The average K^+ conductance (7.6 nS) is shown by the broken lines; fluctuations about that average value are shown for five independent simulations. Experimental data such as those simulated here can be characterized mathematically and used to examine the effects of channel noise under non-voltage-clamped conditions.

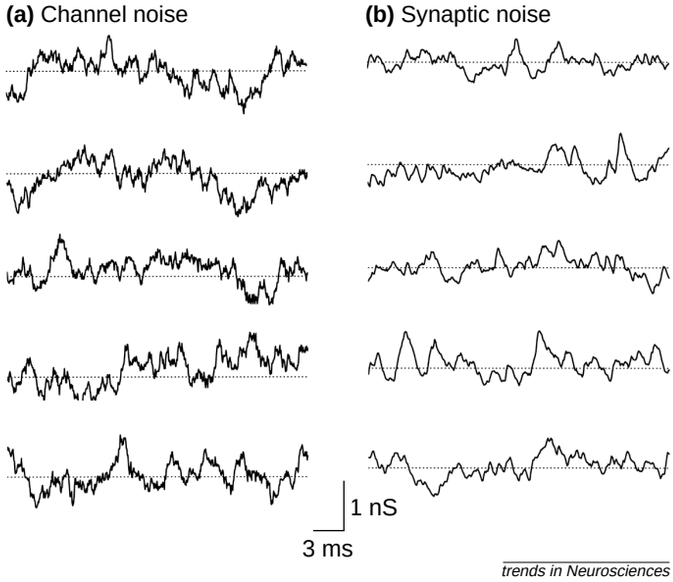

Fig. I. ***Simulated biological noise.*** *Five independent examples of stochastic conductances generated by simulated voltage-gated ion channels* **(a)** *and synaptic processes* **(b)**. *The average steady-state conductance is shown by the broken line in each trace.*

Noise from synaptic processes is more complex than channel noise, because it arises from multiple sources. Among the potentially important sources of synaptic noise are the fundamentally probabilistic nature of quantal release, the random nature of diffusion and chemical reactions within the synaptic cleft, and the unpredictable responses of ligand-gated ion channels. Another significant source of variance in the synaptic signal received by the postsynaptic neuron comes from the firing patterns of presynaptic neurons, which often show random behavior. Realistic quantification of synaptic noise requires *in vivo* intracellular recordings. Figure Ib shows simulated synaptic noise, generated by a population of 1000 independent inputs, each of which fires randomly with average firing rate 10 spikes/s. Each presynaptic spike generates a conductance change with rising time constant 0.1 ms, falling time constant 1 ms. Synaptic events are represented using a Poisson-distributed quantal model, with a mean number of released quanta equal to 10 and single-quantal conductance changes of 10 pS. The mean value of the synaptic conductance (dotted lines) is 9.1 nS.

Synaptic noise is believed to be the dominant factor that limits neuronal reliability under many circumstances[c–f], but channel noise might make important contributions under some circumstances. For example, conditions of summation of many independent excitatory inputs without counterbalancing inhibitory inputs might make synaptic variance relatively low[g]. Alternatively, conditions under which a population of less than 10^5 voltage-gated channels has a crucial role in determining threshold[h] can make the spike generation process particularly noisy. Finally, the effects of channel noise in limiting reliability can be enhanced when the frequency content of synaptic input does not match preferred firing rates[i,j].

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With very few exceptions, the single-neuron modeling community makes the implicit assumption, which is embedded in their choice of Hodgkin–Huxley-type models, that the random behavior of a population of voltage-gated channels can be ignored. This decision can be made by assumption (that N is a very large number or that synaptic noise is so large that it dominates the neuronal response), or by simple oversight. Such model formulations give deterministic responses, although they allow the possibilities of chaotic responses (that is, responses that are very sensitive to initial conditions) or noisy responses that reflect the random behavior of synaptic input. The evidence supporting another view, in which the random behavior of voltage-gated ion channels is sufficient to alter neuronal input–output relationships and intrinsic dynamics, is reviewed in this article.

How large is large?

It is commonly assumed that, at the cellular level, conductances should be essentially deterministic because their size (~1–10 nS for a mammalian neuron) exceeds the conductance of single channels (1–100 pS) by two to four orders of magnitude. Surely one should be able to ignore random fluctuations in a population of tens of thousands of channels.

Perhaps surprisingly, the answer to this question is 'no' in many cases. Early evidence to support this assertion came over 60 years ago, when Pecher demonstrated that neurons do not exhibit a precise threshold[10]. If the probability of firing in response to a brief current pulse is estimated as a function of input amplitude, the resulting curves do not show a step-like transition to unity firing, as do the classical Hodgkin–Huxley equations, but typically show a graded transition (Fig. 1a,b), the width of which is quantified by a factor called 'relative spread' (Fig. 1b). Later work by Verveen[11,17] began the process of quantifying neuronal noise sources that were likely to contribute to relative spread. Building on this work, Lecar and Nossal used techniques from statistical physics to make a precise analytical linkage between channel noise and relative spread (Fig. 1c)[12,13]. The capstone of this effort was provided by an experimental

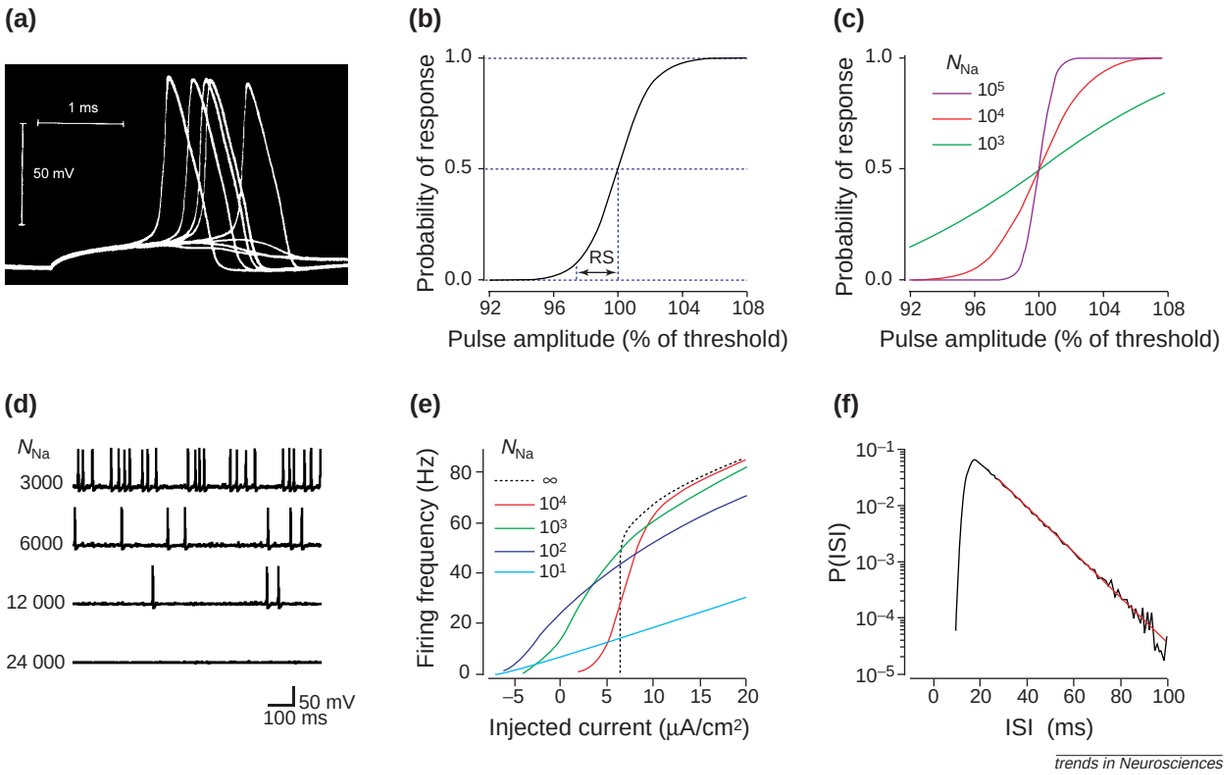

Fig. 1. ***Channel noise gives rise to uncertainty in threshold.*** **(a)** *Responses of a node of Ranvier from frog sciatic nerve to repeated stimulation at threshold intensity (defined as the current magnitude that gives a probability of suprathreshold response of 0.5) are shown. Eight sweeps are superimposed. The interstimulus is 2 s and its duration is 5 ms.* **(b)** *A typical plot of estimated probability of response versus normalized current magnitude for a nerve fiber. Threshold defined as in* (a). *Relative spread (RS), a measure of the width of the curve, is obtained from fitting the function* $-0.5\{1 + erf[(I\% - 50)/RS]\}$, *where I% is current pulse amplitude (as a percentage of threshold) and*

$$erf(x) = 2/\sqrt{\pi}\int_0^x e^{-\lambda^2} d\lambda$$

is the so-called error function. **(c)** *Predicted probability of response versus stimulus amplitude for nodes of Ranvier of four sizes. Relative spread is proportional to* $N_{Na}^{-1/2}$, *where* N_{Na} *(the number of* Na^+ *channels) is determined by the size of the patch of membrane simulated. This method of scaling allows one to change the level of noisiness while leaving all other factors constant.* **(d)** *Sample plots of stochastic Hodgkin–Huxley models at rest. As* N_{Na} *is increased, the model becomes less prone to spontaneous activity; for* $N_{Na} > 20\,000$ *the model is silent at rest, as is the deterministic Hodgkin–Huxley model.* **(e)** *Plots of firing frequency versus applied current from stochastic and deterministic simulations of squid giant axon. Firing rate changes more gradually with applied current as the number of channels decreases, as does relative spread (data not shown).* **(f)** *The normalized interspike-interval (ISI) histogram for a stochastic Hodgkin–Huxley model with no applied current* ($N_{Na} = 600$). *Interspike-interval statistics resemble those of a memoryless process with exponentially distributed intervals and a refractory period (indicated by the low number of short intervals).* (a) Adapted, with permission, from Ref. 11, (b) adapted, with permission, from Ref. 10, (c) plotted from equations derived in Refs 12,13, (d) adapted, with permission, from Ref. 14, (e) adapted, with permission, from Ref. 15, and (f) adapted, with permission, from Ref. 16.

demonstration by Sigworth that channel noise is sufficient to account for non-deterministic neuronal thresholds[18].

Computational approaches to tackle this problem began around 1980, when researchers gained access to modern computer-processing power. To our knowledge, the first such effort was performed by Skaugen and Walløe (Fig. 1e), in a study that is remarkable for its completeness[15]. Additional studies have concluded again and again that channel noise affects the dynamics of neuronal systems, even when the number of channels involved exceeds 10 000 (Refs 14,19–25). Interspike-interval histograms for the stochastic Hodgkin–Huxley equations are exponential with a refractory period (Fig. 1f). Intervals show no dependence on past events, either in the case of spontaneous[14,16] or driven[26] activity. Imparting voltage-gated channels with the 'memory' of how long they have been closed or open can induce long-term trends in interspike-interval statistics[16].

Several factors help to account for the surprisingly large effects of channel noise in modeled neurons. First, diminution of the *CV* of a given conductance with increasing *N* decays only proportionally to $N^{-1/2}$ (Eqn 3). Second, contributions of channel noise often come at relatively hyperpolarized potentials with correspondingly low probabilities of opening[24]. Under these conditions, the *CV* associated with a given conductance is large. (Note that $CV \to \infty$ as $p \to 0$.) Third, random openings of Na^+ channels at potentials that are close to resting potential depolarize the cell, which further increases the probability of opening of these channels[14,25]. Thus, the regenerative 'positive feedback' phenomenon that leads to action-potential generation also serves to amplify the effects of random openings of Na^+ channels.

Reliability in response to time-varying stimuli

Most early work focused on responses of neurons to pulses or step changes in direct current (DC). More-recent work has examined responses to repeated presentations of fluctuating stimuli, usually single examples of a filtered, pseudo-random signal. This approach has the advantage that the stimuli in question are realistically broad in their frequency content. However, the broad-band approach has the disadvantage that it can be difficult to interpret data sets that contain mixtures

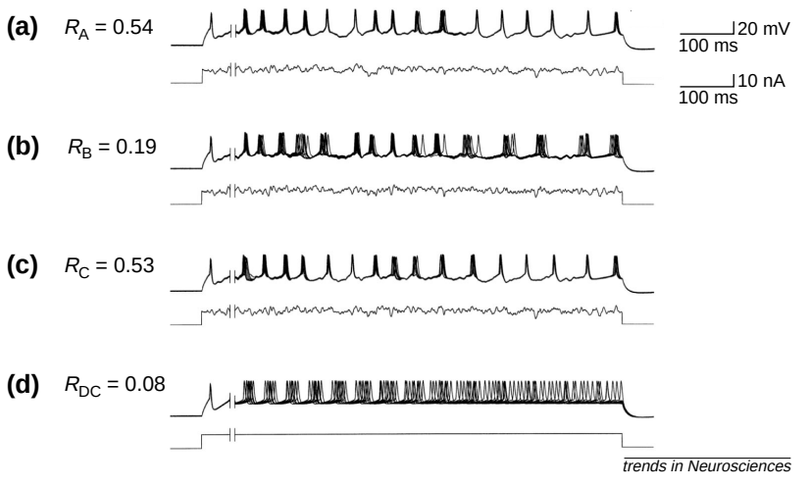

Fig. 2. ***Stimulus frequency content affects neuronal reliability.*** *Superimposed responses of a buccal motoneuron from* Aplysia californica *to repeated presentations of fluctuating current stimuli with different frequency content are shown (from the work of Hunter and colleagues[32]). The four stimuli were broadband* **(a)***; band-reject, with the excluded frequencies near the preferred firing frequency of the neuron corresponding to the direct current (DC) level of the stimulus* **(b)***; band-reject, with the excluded frequencies below the preferred firing frequency of the cell* **(c)***; and DC* **(d)***. Calculated levels of reliability (R_A, R_B, R_C, R_{DC}) are shown for each case. Reliability is highest in response to stimuli that include frequency content close to the preferred firing frequency of the cell.* Reproduced, with permission, from Ref. 32.

of qualitatively different responses to short stimulus sequences of different magnitudes[27]. Recorded and simulated responses to filtered white noise[24,28,29] show reliability that depends on the degree of fluctuation in the input signal, with high reliability corresponding to large fluctuations. Reliability also varies with frequency content of the input signal[24,30]. In particular, neurons fire most reliably in response to stimuli with significant frequency content that matches their expected firing rate in response to the DC component of the input[31,32]. The effect of frequency content of fluctuating signals on reliability is exemplified by the data in Fig. 2.

Channel noise in oscillatory neurons

Recent work has included studies of cells with more-complex electrophysiology than that of the squid giant axon. For example, stellate neurons of the mammalian medial entorhinal cortex (MEC) exhibit both action potentials, which are generated by a fast Na^+ conductance and delayed rectifier K^+ conductance, and slow subthreshold oscillations, which are generated by a persistent (non-inactivating) Na^+ conductance and very slow opposing conductance[33–35]. The persistent Na^+ conductance is generated by a few thousand channels[25] and is the major noise source in these cells (with the possible

Box 2. Modeling methods for populations of stochastic ion channels

Stochastic ion channels are typically represented as memoryless chemical reactions with transition rates that depend instantaneously on membrane potential[a]. The simplest such description would be a two-state system:

$$\text{Closed} \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftarrows}} \text{Open}$$

where $\alpha(V)$ and $\beta(V)$ are the voltage-dependent transition rates. Two modeling methods have been used for modeling systems of stochastic, voltage-gated ion channels. In the first, the states of individual gating particles or ion channels are tracked with either a varying or constant timestep, Δt. The current-balance equation is integrated over Δt. States of each channel are updated according to the appropriate probability functions[a]. This process is repeated for the length of the simulation. This method is conceptually simple and very accurate, as long as the random-number generator is adequate and Δt is small compared with the speed of fluctuations in membrane potential or channel state. (A clear and concise review of the complex subject of random-number generators is given by Press and colleagues[b]. A basic tenet to bear in mind is that default random-number generators typically perform poorly.)

In practice (data not shown), Δt must be very small (~1 μs) to simulate events in spiking neurons accurately, probably because state transitions in Na^+ channels are very rapid. The first method requires a significant amount of 'bookkeeping' to track the state of each channel or particle. More importantly, this method is inefficient: even for a population of N ion channels with only two states, this method requires generation of N random numbers and several logical comparisons per time step.

In the second method of modeling stochastic neurons[c,d], efficiency is increased by taking advantage of the presumed independence and memoryless nature of individual ion channels. In this method, the programmer keeps track not of the states of each channel but rather the total number of channels in each state. The time interval Δt until the next state transition is drawn from a probability function representing all possible transitions. The system of differential equations is integrated over Δt. The identity of the event is established and the channel counts are updated accordingly, then the next state transition time is selected. For a set of N channels governed by Eqn 1, the algorithm is simple:

(1) Specify initial values of V, the number of open channels N_o, and the number of closed channels $N_c = N - N_o$.
(2) Calculate the effective rate for the next state transition, $\lambda = (N_c\alpha + N_o\beta)$.
(3) Generate two random numbers r_1 and r_2, uniformly distributed between 0 and 1. The time of the next state transition is:

$$\Delta t = \frac{1}{\lambda}\ln\left(\frac{1}{r_1}\right)$$

(4) Integrate the entire set of differential equations from current time t to new time $t + \Delta t$.
(5) Choose Reaction 1 (a channel closing) if $N_o\alpha \geq r_2\lambda$. Otherwise, choose Reaction 2 (a channel opening). Update N_o and N_c.
(6) Go to Step 2.

For more-complex channel-gating schemes, the algorithm operates by similar principles[d,e]. This second method is more computationally efficient than the first because only two random numbers are needed per timestep, even for channels with very complex rate equations. The accuracy of the second method depends on generation of high-quality random numbers, as does the accuracy of the first method. The variable time step Δt should be kept sufficiently small so that membrane potential (and hence transition rate constants) do not change much during a given timestep. In practice, this constraint is usually met automatically, because even systems that consist of small numbers of channels switch states very frequently.

Other methods have been proposed that rely on a Gaussian approximation of channel-noise terms[f]. These methods have not yet been implemented and tested in the literature for stochastic neuronal models.

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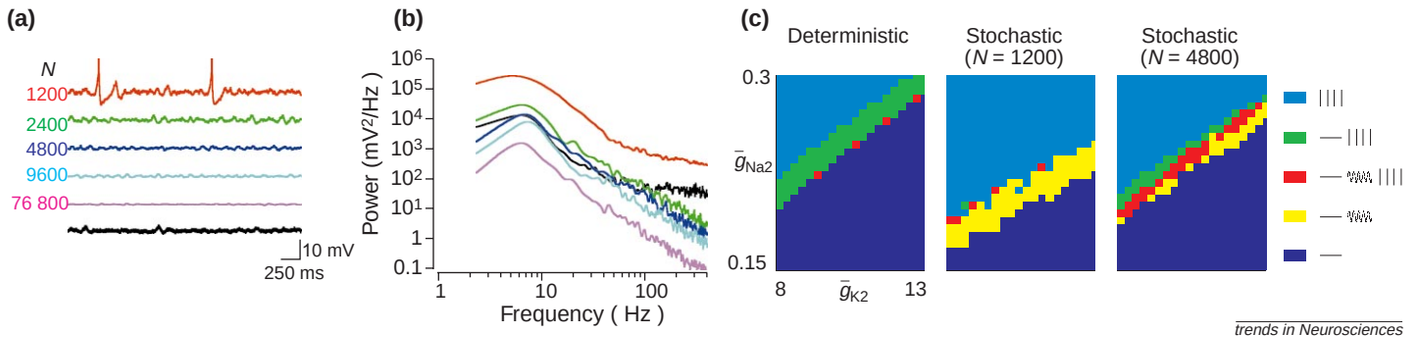

Fig. 3. ***Channel noise increases excitability and allows a broader repertoire of behavior in models of entorhinal cortical neurons.*** **(a)** *Colored traces show simulated responses to modest depolarization, with* N, *the number of persistent (non-inactivating) Na^+ channels (shown on the left), varied from 1200–76 800. Changes in* N *were effected by changing the size of the piece of membrane simulated, leaving all factors except the level of channel noise unchanged. For* N = *1200, the model cell fires action potentials (truncated); for larger values of* N, *the cell exhibits noisy subthreshold oscillations but no action potentials. The black trace shows experimental current-clamp data at the same mean potential (−54 mV).* **(b)** *Power spectra of the traces in* (a) *[colors are the same as those used in* (a)*]. Spectra are the average power from a series of 14 short-time, 1024-point fast Fourier transforms (FFTs), calculated from a data trace of 3 s duration. Data windows were shifted 512 points for each iteration of the short FFT. For each data segment, the mean potential was subtracted away and a Hamming window was applied.* **(c)** *Maps of qualitative behavior as a function of the maximal values of the persistent Na^+ conductance ($\bar{g}_{Na2}$) and slow K^+ conductance ($\bar{g}_{K2}$) for three model types. Changes in $\bar{g}_{Na2}$ or* N *were effected by changing the size of the membrane area that was simulated, thus leaving all other aspects of the model unchanged. Behavior was mapped by applying currents of 0–3 $\mu A/cm^2$ and measuring, on individual responses, the ratio of alternating current (AC) power to total power and the probability of spike generation per subthreshold cycle. The AC power-ratio threshold for subthreshold oscillations was 1.4×10^{-4}, equivalent to a 1 mV sinusoid superimposed on a membrane potential of −60 mV. The threshold for reliable spiking was a probability of 0.1 per cycle. The color-coded regions represent five types of qualitative behavior over the range of direct current (DC) levels. Region 1 (dark blue) represents models that are silent for all levels of DC current injection. Region 2 models (yellow) are silent at resting potential and generate subthreshold oscillations with depolarization, but do not generate action potentials. Models from Region 3 (red) replicate the varied behavior seen in electrophysiological recordings; they are silent at rest, generate subthreshold oscillations with moderate depolarization, and generate action potentials at higher levels of depolarization. Region 4 (green) contains models that are silent at rest and spike with depolarization, but do not generate subthreshold oscillations at any level of depolarization examined. Finally, models in Region 5 (light blue) fire spontaneously. With too little noise (left panel), the model almost never generates subthreshold oscillations. With too much noise (middle panel), subthreshold oscillations (yellow) and spikes (light blue) are prominent, but physiologically relevant Region 3 behavior (red) is rare. With* N = *4800 (right panel), the noise level is appropriate to allow a wider range of behaviors. In particular, this value of* N *and associated noise level give reasonably robust Region 3 (red) behavior (silence, subthreshold oscillations and spiking for one point in parameter space) that matches physiological data.* Adapted, with permission, from Ref. 25.

exception of synaptic noise, which is not prominent *in vitro* but might be much more conspicuous *in vivo*).

MEC stellate cells can be described adequately using a one-compartment cellular model with a stochastic representation of the persistent Na^+ conductance (see Ref. 25 and Box 2 for details) and deterministic elements for the other three nonlinear conductances[25] (some results are shown in Fig. 3a,b). Modeled and experimental results match best for $N \sim 5000$. These results imply that neurons with small numbers of channels are more noisy and more excitable, and that these characteristics can be used to estimate channel numbers in stochastic neuronal models.

In addition to increasing excitability, intrinsic channel noise can alter neuronal dynamics in more-complex ways. Figure 3c shows color-coded 'maps' of the range of dynamical behaviors exhibited by the MEC model over a large parameter range. The *x*- and *y*-axes represent the sizes of the slow K^+ and persistent Na^+ conductances, respectively. The three maps represent behavior of the deterministic model, along with stochastic models of two different noise levels. The presence of channel noise alters the dynamical behaviors that a given model can exhibit. In particular, the MEC model generates subthreshold oscillations and action potentials most readily for only intermediate noise levels ($N = 4800$).

Channel numbers and cellular economy

In determining optimal channel numbers (not to mention channel locations), neurons face several complex constraints, some of which are conflicting. First, channels of opposing action must be incorporated into the membrane in the correct densities and proportions in order to achieve the appropriate electrophysiological properties. A striking example of this phenomenon is shown in Fig. 4, which contains histograms that represent the probabilistic distributions of resting membrane potential for *Xenopus* oocytes containing high (Fig. 4a) and low (Fig. 4b) densities of voltage-gated K^+ channels. High channel densities yield a stable value of resting potential, which is determined by the activation and deactivation kinetics of the channels[36]. With low channel densities, activation and inactivation properties of the channels interact to produce large fluctuations in resting potential[36]. Second, axonal-conduction velocities vary as a function of channel densities. In non-myelinated axons, for example, the theoretical relationship between conduction velocity and Na^+-channel density is bell-shaped, with a peak value near the measured density found in the squid giant axon[37,38]. Third, channel numbers are related intimately to neuronal reliability, which must have an important role in constraining coding schemes. Fourth, large channel numbers imply a large energetic investment, not only because of the cost of the proteins, but also because large ionic currents imply a greater accumulation of ions and thus increased demand on ion pumps. The energetic cost per action potential or per 'bit' of information can be considerable[39], making this constraint potentially extremely important. Indeed, it has been suggested that anoxia-tolerant animals use reduced channel numbers in order to keep oxygen demand low[40]. How nerve cells deal with the delicate balancing act of reliably coding information on a tight metabolic budget is a topic that merits further investigation.

Future directions: experimental and theoretical

The evidence that channel noise affects neuronal dynamics is intriguing, but more research is needed. Experimentally, three recently developed methods

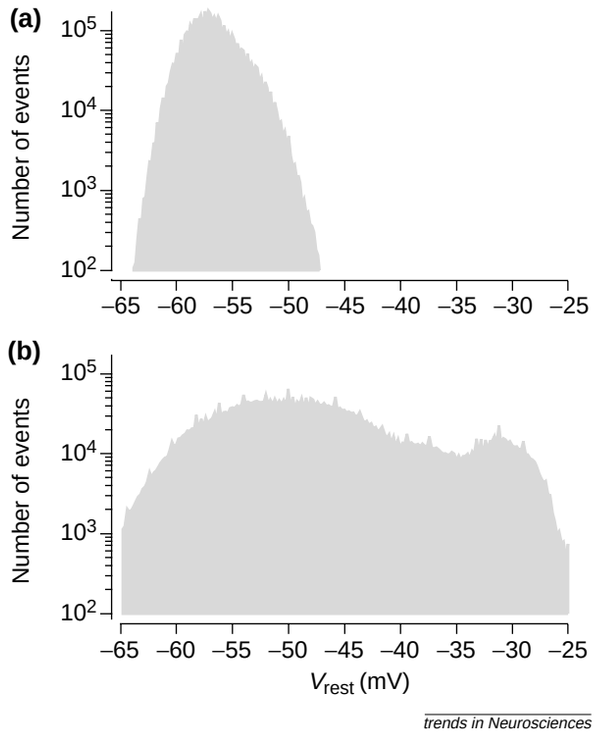

Fig. 4. ***A significant number of K^+ channels is necessary to stabilize membrane potential in expression systems.*** *Amplitude histograms of 'resting' membrane potential, obtained from current-clamp recording of inside-out patches in* Xenopus *oocytes that contain Shaker K^+ channels. Channels were modified to eliminate fast inactivation, but still exhibited slow inactivation. In patches with high channel density [***(a)**, N *~5000)], membrane potential was relatively stable at a value that could be determined analytically from voltage-clamp data and knowledge of leak characteristics. Slow inactivation properties of K^+ channels are unimportant in determining resting potential. In patches with low channel density [***(b)**, N *~20], membrane potential is unstable and dependent on slow inactivation of K^+ channels.* Modified, with permission, from Ref. 36.

should allow the effects of channel and other noise sources to be studied directly. First, the correlation of single-channel events and spike initiation, recorded under cell-attached patch-clamp, is an ingenious and powerful technique for examining the effects of single-channel events at the whole-cell level[41–43]. Second, ion-channel expression systems (for example, *Xenopus* oocytes) allow experimentalists to compare quantitatively the response properties of cells with measurably different numbers of voltage-gated channels. This approach has been exploited to study the relationship between channel numbers and the stability of resting potential (Fig. 4)[36]. Third, elaborations of the dynamic-clamp technique[44] might allow researchers to examine the effects of well-controlled, artificial noisy conductance sources in the living cell[45].

In the struggle to understand the implications of biological noise sources, neurobiologists would be wise to recognize that theoretical results from physics and mathematics have much to offer. For example, results from stochastic differential equations and statistical mechanics have been applied successfully to the analysis of neuronal noise sources on several occasions[12–14,46]. Another promising avenue of research would involve extending the pioneering work of Laughlin and colleagues[39] in order to understand the relationships between channel density, information content and metabolic cost.

In parallel with experimental and theoretical efforts to quantify channel noise, there should also be efforts aimed at exploiting its presence for practical gain. Box 3 describes early efforts to use channel noise as a potentially useful surrogate for synaptic noise in cochlear implants.

Concluding remarks

Electrical noise from voltage-gated ion channels is invariably present and measurable. Together with noise

Box 3. Clinical implications of channel noise

Channel noise in neurons, a seemingly esoteric topic of study, could have practical implications in improving the performance of cochlear implants, widely used devices that mitigate severe hearing loss by electrically activating the deafferented spiral ganglion[a]. Under normal conditions, release of neurotransmitter from inner hair cells (IHCs) is stochastic, with a high rate of spontaneous release. Spontaneous and driven activity in auditory nerve fibers are known to be noisy and uncorrelated[b–d]; the noisy release process is likely to be a significant contributor to these properties. By contrast, electrically stimulated auditory nerve fibers in patients with hearing loss lack spontaneous activity and have driven responses that are largely deterministic and correlated statistically across the population[e]. The lack of spontaneous activity might contribute to the tinnitus commonly reported in people with sensorineural hearing loss[f]. Insufficient independence of activity in auditory nerve fibers could also rob the electrically stimulated auditory system of distinct coding advantages offered by statistically independent populations[g,h].

In attempts to generate noisy, statistically independent responses in electrically stimulated auditory nerve fibers, one intriguing line of research relies on the only natural source of stochasticity that remains in the deafferented, electrically stimulated system: channel noise from voltage-gated ion channels in auditory nerve cells[i]. Under current electrical-stimulation protocols used in cochlear implants, this noise is masked. However, both computational simulations and compound-action-potential recordings[j] indicate that high-frequency (5 kHz) electrical stimulation can 'amplify' channel noise and create responses in a population of auditory nerve fibers that closely resembles those normally produced by the IHC synapse. High-frequency stimulation might provide a way to induce statistically independent spontaneous and driven activity, and thus enhance performance in cochlear implants.

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from synaptic sources, it must be considered in any conceptual model of the nervous system. Noise in the nervous system might have a number of roles. For example, biological noise almost certainly constrains coding accuracy in many neuronal structures[4,47]. It might expand the repertoire of dynamic behaviors of some neurons[24,25], and enhance signal detection under some circumstances[48]. Changes in noise level, which are attributable to temperature or electric-field gradients, can lead to detectable changes in the firing patterns of multimodal sensory cells[49,50]. Finally, noise can improve the performance of artificial neuronal networks designed to solve specific optimization problems (for example, simulated annealing) by helping the system escape from local minima[51].

The results reviewed in this article are specific examples of a more-widespread phenomenon: the role of noise in nonlinear biological systems. Effects of noise seem particularly likely to be found in sub-cellular signaling pathways, including those involved in second-messenger systems and regulation of gene expression, because these systems include a relatively small number of constituent molecules that interact nonlinearly. The implications of noise in normal and pathological cellular biology have only begun to be explored[52–54]. The broadening of our knowledge of electrical fluctuations should also contribute to this new field of cellular biology.

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