

Getting the most out of noise in the central nervous system

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Rather than merely a nuisance, noise in biological systems is a useful property. Before patch-clamp methods were invented, analysis of membrane current noise provided the first solid, if indirect, evidence for the existence of ion-conducting pores with discrete conductance levels. Although supplanted by single-channel recording techniques for most tasks, analysis of current membrane noise remains useful for certain problems, such as determining the properties of channels with rapid kinetics that open with a high probability and desensitize, channels localized at synapses, channels with an unusually low unitary conductance and open-channel noise. In addition, the role of noise in information processing in the CNS is increasingly being recognized. In this article, we summarize the analysis of current membrane noise with an emphasis on what the technique is still useful for, and discuss the role for noise in information processing.

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The application of noise analysis to biological processes provides an invaluable example of technology transfer. It is useful to consider such examples in a world of increasing specialization, because they remind us that advances can accompany the transfer of ideas between dissimilar fields. In 1966, Verveen and Derksen¹ published an intriguing investigation of membrane noise aimed at understanding the probabilistic behavior of neurons in the CNS. By describing a potential role for noise in computation, this pioneering work changed the prevalent view in biology of noise as a bothersome phenomenon. The focus on noise was expanded in 1970 when Katz and Miledi² sought a means for analyzing the signal fluctuations that accompanied ACh receptor-mediated muscle depolarization²⁻⁵. Investigators studying these topics found that previous work had established the idea that the properties of random unitary events could be extracted from the fluctuating or 'noisy' signals that arose from the summation of many such events. These groups drew on fluctuation theories that were originally developed to describe and usually minimize noise in electrical circuits, cathode ray tubes, telegraph signals, nuclear physics and molecular collisions in gas phase. This information facilitated the formulation of theories describing the origins and analysis of some (but not all) biological noise, and the application of these theories to experimental data provided insight into the nature of transmembrane-conductance changes and information processing in the brain. In this article we update these two applications of noise analysis to neurobiology. First, we review the analysis of membrane-current fluctuations and explain what it is still useful for, now that single channel recording is widely accessible. Second, we discuss how the CNS can utilize noise, which carries no signal information, to enhance signal detection through a phenomenon known as stochastic resonance. The work across these fields is enormous. Here we touch on the work of only a few, referring the reader to several excellent reviews⁶⁻¹⁰.

Noise analysis of membrane-current fluctuations

Noise analysis was first used to evaluate the idea that transmembrane currents were carried by ion channels with aqueous pores, each capable of passing the same unitary current when open. The first results suggested that membrane currents originate from the summation of many small currents, a finding that supported the existence of ion channels³⁻⁵. From this introduction in the 1970s, analysis of macroscopic current fluctuations has often been used by investigators to estimate the single-channel conductance of ion channels. In addition, some investigators have successfully used noise analysis to study ion channel kinetics. However, now that single-channel recording is commonplace and provides results that are more readily interpretable, is noise analysis merely a historical footnote? Not yet, because some old problems persist and new ones have arisen for which single-channel recording or analysis is impossible. Because of the utility of noise analysis in these situations, we review the two features of noise that can be measured from macroscopic currents: amplitude and frequency composition.

Estimation of unitary current and open probability of channels from variance analysis

The goal of variance analysis is to infer properties of the unitary currents passed by the individual channels that underlie a given current from the fluctuations about the mean amplitude of that current. Discussion here will be restricted to voltage-clamp recordings of ohmic channels. This is accomplished by exploiting the probabilistic nature of channel function in order to gain information about the channels themselves. Because the duration of individual channel openings is random, a membrane containing 100 channels that are open on average half of the time will have, for example, 40 channels open at one time and perhaps 60 an instant later. The moment-to-moment fluctuations in the number of open channels are governed by the physical properties of the channel that define its function. This means that we can extract information

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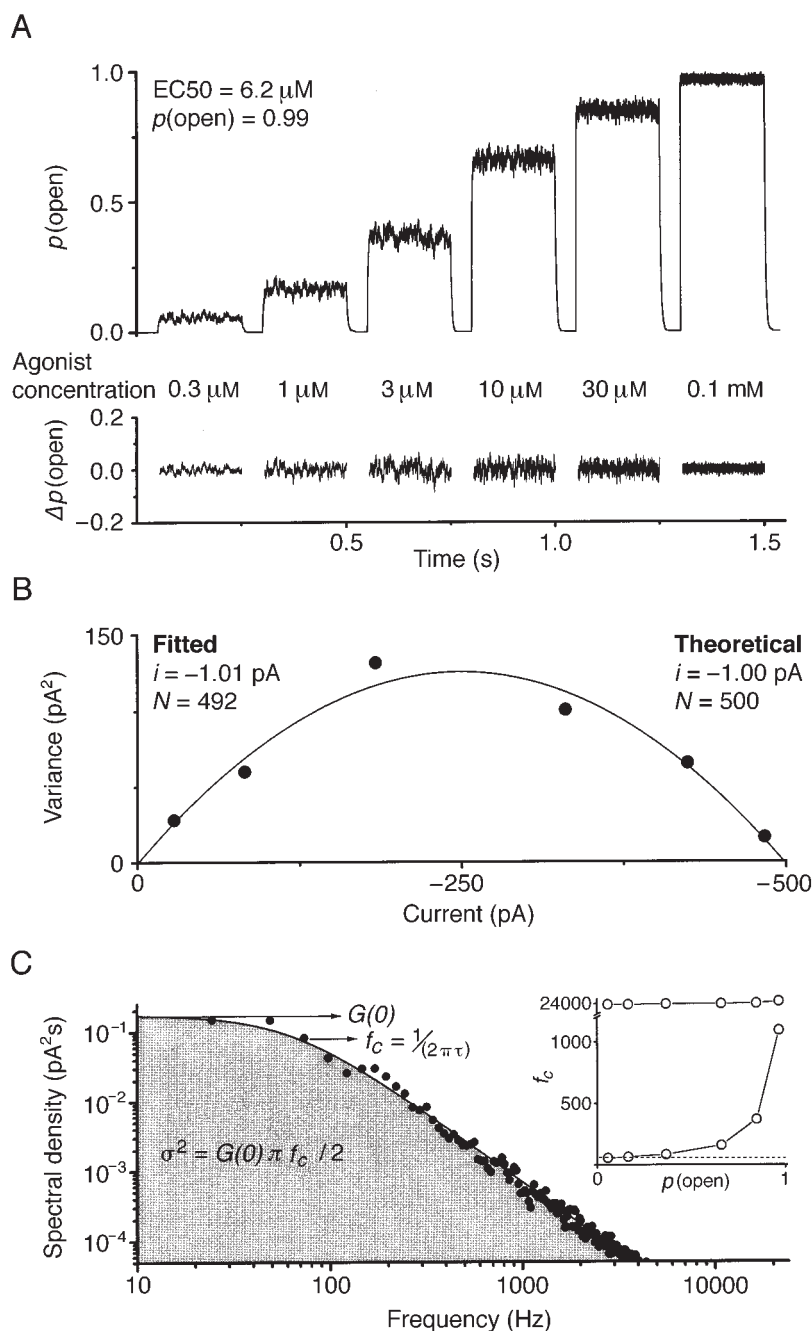
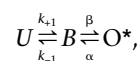


Fig. 1 (A) Current responses were simulated for a ligand-gated channel that opened in bursts according to:



where *U* is the unbound closed state, *B* is an agonist-bound closed state, and *O** is an agonist-bound open state ($k_{+1}=1 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$, $k_{-1}=5 \times 10^4 \text{ s}^{-1}$, $\beta=1 \times 10^5 \text{ s}^{-1}$, $\alpha=1 \times 10^3 \text{ s}^{-1}$). The responses of five hundred 10 pS channels to different concentrations of activating agonist are shown as the channel open probability [p(open)]. The different amplitude and frequency composition^{6,7} of current fluctuations are readily apparent for responses of different amplitudes; the fluctuations are isolated in the lower trace. **(B)** The variance of the current fluctuations (V_{HOLD} of -100 mV; V_{REV} 0 mV) is plotted against the response amplitude. The curve is the expected variance from Eqn 1 for 500 channels with a conductance level of 10 pS. **(C)** A power spectrum is shown for 1000 of these receptors, activated by 0.1 μM agonist (filled circles). At this concentration, p(open) is low and the spectrum is dominated by a single Lorentzian component that has a fitted cut-off frequency ($f_c=63 \text{ Hz}$, lower arrow) that corresponds to a mean burst length of 2.5 ms, similar to that expected (3.0 ms). A second component ($f_c=24 \text{ kHz}$) exists, but is difficult to observe given its small amplitude and the resolution of the simulation (10 μs). The solid line is a single Lorentzian function (Eqn 4) fitted to the data; the upper arrow shows the asymptotic spectral density. The variance of the signal can be calculated from the area under the curve (gray fill). The inset shows the changing cut-off frequencies (open circles) for the two components of spectra obtained from responses as in (A) plotted as a function of p(open). The high frequency asymptotic spectral density was always less than 1% of that for the slow component. The dotted line is the cut-off frequency corresponding to the mean burst length.

another^{7,10}. For a cell containing *N* channels that each pass a current of amplitude *i* when open, the mean current (*I*) is:

$$I = i N p$$

and variance (σ^2) is:

$$\sigma^2 = i^2 N p (1-p)$$

where *p* is the probability that the channel is open. Combining these two equations and substituting for *p* yields:

$$\sigma^2 = i I - (I^2 / N) \tag{1}$$

about how a channel works from statistical analysis of these current fluctuations.

Intuitively, how does variance analysis work? Figure 1A shows a dose–response curve for a ligand-gated channel whose structural conformations can be categorized into three functionally distinct sets. The isolated current fluctuations of the response at low and high concentrations of agonist are minimal because most of the channels are in the open or closed state. However, at the intermediate agonist concentrations, there are larger current fluctuations. At half of the maximally effective concentration of agonist, there is the maximum moment-to-moment variation in the number of open channels, because the half that are open randomly close and the half that are closed randomly open.

The relationship between the variance and the unitary current amplitude can be derived from the binomial theorem, making the usual assumption that channel transitions occur independently from one

Equation 1 suggests, as has been found experimentally, that a plot of the current variance versus current amplitude is parabolic (Fig. 1B). Fitting the relationship constructed from analysis of different magnitude responses with Eqn 1 can provide an estimate of the unitary current and the number of channels from which single channel conductance (γ_{NOISE}) can be determined from Ohm’s Law if the reversal potential is known. In addition, an estimate of the maximum open probability of the channel, *p*(open), can be obtained by dividing the experimentally determined response by the theoretical maximum response, which is the product of the unitary current and number of channels in the patch (*i N*). Although determination of *N* and *i* is robust for channels with *p*(open) values greater than 0.4, reliable estimates of *N* are difficult to extract from the current–variance curve when *p*(open) is low and the relationship between current and variance is approximately linear:

$$\sigma^2 \approx i I \quad (2)$$

An important assumption when calculating the variance from Eqn 1 is that the current is stable over the time the variance is determined, because slow changes in macroscopic response amplitude or modal shifts in channel gating introduce errors into variance and spectral analysis (see Refs 6–8,10 for reviews).

The unitary current i for a channel can also be obtained directly from single-channel records; however, $p(\text{open})$ cannot be determined unless the number of channels in the membrane patch is known. Values for $p(\text{open})$ can be obtained from noise analysis regardless of how many active channels are in the patch, but the statistical nature of this approach means that many responses must be analyzed collectively. Thus, differences in unitary current amplitudes that arise from subconductance levels or receptor heterogeneity are lost in the composite conductance value γ_{NOISE} obtained from variance analysis. In this situation, a general expression describes the variance of receptors with k sublevels^{6,11}:

$$\text{Variance} = N V^2 \left[\sum_{j=1}^k p(\text{open})_j \gamma_j^2 - \left(\sum_{j=1}^k p(\text{open})_j \gamma_j \right)^2 \right] \quad (3)$$

where V is the transmembrane potential, and $p(\text{open})_j$ and γ_j are the steady-state open probability and conductance for sublevel j . If the sublevel conductances are known, this expression can be used to estimate $p(\text{open})_j$ from the experimental current–variance relationship¹². The contribution of each sublevel conductance to the mean conductance, γ_{NOISE} , is weighted by its frequency and amplitude ($p_j \gamma_j$), that is, the fraction of current that flows through it. When $p(\text{open})$ is low, the γ_{NOISE} can be calculated by simplifying Eqns 2 and 3 (Refs 7,11,13):

$$\gamma_{\text{NOISE}} \approx \sum_{j=1}^k N_j p_j \gamma_j^2 / \sum_{j=1}^k N_j p_j \gamma_j$$

Estimation of kinetic parameters from spectral analysis

Intuitively, a relationship must exist between the nature of the current fluctuations and the mean time a channel stays open. Channels that stay open for brief periods of time produce rapidly fluctuating currents, whereas channels with longer open times produce slowly fluctuating noise. Thus, the frequencies of fluctuations buried in the noise contain information about the mean channel open times, provided that transition rates are constant, that is, agonist concentration or holding potential (V_{HOLD}) is constant. There are two ways to exploit this. First, and perhaps most intuitive, the covariance of the signal can be calculated: this is, the correlation between values of a signal at different times, such as t and $t + \Delta t$. If a time interval Δt is small, the currents should be correlated because there is a high probability that channels that are open or closed at time t will remain open or closed at $t + \Delta t$. However, as the time interval Δt lengthens, the correlation diminishes because multiple channel openings become increasingly likely to occur within the time interval. The covariance function $C(\Delta t)$ for a channel with one open and one closed state contains an exponential term that arises from the conditional

probability that a channel open at t is also open at $t + \Delta t$ (Ref. 10), and is:

$$C(\Delta t) = N i^2 p \exp(-\Delta t / \tau)$$

where τ is the time constant of relaxation, or the reciprocal of the sum of the forward and backward rate constants. At low $p(\text{open})$, the forward rate constant is negligible and τ is simply the reciprocal of the closing rate or the mean channel open time. For a channel with n kinetically distinguishable states there are $n-1$ components of the covariance function. Thus interpretation of τ becomes more complex, particularly at higher $p(\text{open})$ values^{6,7} (Fig. 1). Second, an estimation of the frequency composition of the signal could be obtained if we isolated each frequency component, perhaps with a perfect set of bandpass filters. This can be accomplished using a Fourier transform to generate a power spectrum, which immediately conveys how energy (in A^2 s or $A^2 \text{ Hz}^{-1}$) is distributed among the various frequency components that comprise the noise. The covariance function and power spectrum are time and frequency representations of the same phenomenon; they contain identical information. In practice, a noise spectrum is typically calculated by averaging together the spectra from many data subsegments, the length of which is twice the inverse of the lowest non-zero frequency point desired. At low frequencies the signal power is constant and the spectrum is flat (Fig. 1C), whereas at higher frequencies, the signal power drops in proportion to the square of the frequency (referred to as $1/f^2$ noise). The single-sided spectrum for a two-state channel can be described by a Lorentzian function:

$$G(f) = G(0) / \{1 + (f/f_c)^2\} \quad (4)$$

where $G(f)$ is the signal power (or spectral density), $G(0)$ is the asymptotic spectral density at zero frequency, f is the frequency and f_c is the cutoff or half-power frequency. The cutoff frequency is the frequency at which the signal power drops to one-half of $G(0)$, and is related to the current relaxation rate defined by the covariance function ($1/\tau$) by:

$$\tau = 1 / (2 \pi f_c)$$

At low $p(\text{open})$, an estimate of the mean single channel open time can be obtained from τ . When a channel possesses n kinetically distinguishable states, its spectrum can be described as the sum of $n-1$ Lorentzian components.

How does the information extracted from spectral analysis compare with that obtained from single channel analysis? Information about channel open time and kinetics can be directly obtained by measuring the duration of single-channel open and closed periods. By contrast, there are ambiguities associated with the interpretation of noise spectra even for the simplifying assumption that $p(\text{open})$ is low. For example, the variance associated with some Lorentzian components is too low to be detected. In addition, the low-frequency points are notoriously difficult to pin down, and can be contaminated by slow changes in the mean current. Because long stretches of time must be analyzed in order to identify correlations that represent long open times, relatively few correlations

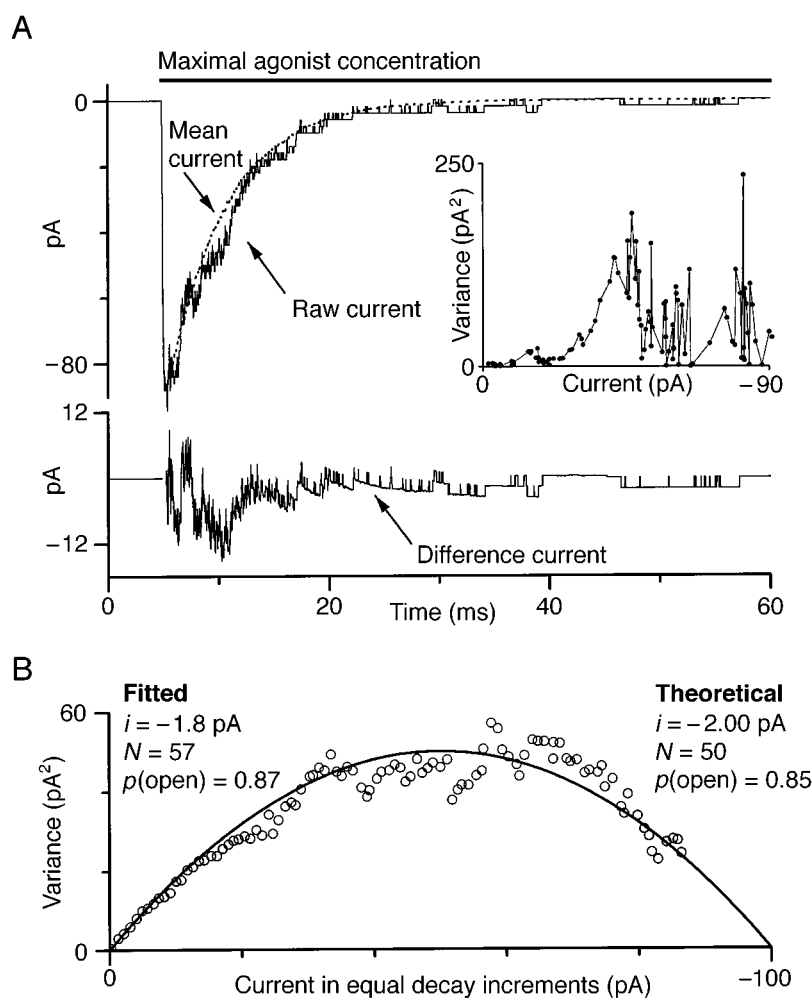


Fig. 2. (A) The upper trace (unbroken line) shows a simulated desensitizing raw current response from 50 receptors (conductance level of 20 pS; $V_{\text{HOLD}} = -100 \text{ mV}$) to the rapid application of a maximally effective concentration of agonist (bar, top). The broken line superimposed on the trace is the mean response for 100 such simulated events. The difference between the mean response and simulated current is shown in the lower trace (rising phase was omitted), and the variance of this residual current is shown in the inset. The variance was calculated from fractions of the decay that were chosen to contain an equal number of channel closures, which ensures that all portions of the variance plot are equally represented¹⁴. The inset shows the relationship between variance of the residual current and the corresponding amplitude of the response. (B) The composite current–variance plot (open circles) obtained from the analysis of 200 simulated responses is smoother than the current–variance relationship from a single response (inset in A), and is superimposed on the theoretical curve (smooth line) predicted from Eqn 1.

between distant data points can be tested in the data record. At the other extreme, rapid gating kinetics cannot be resolved. For this reason, it can be assumed that if intra-burst closed intervals are brief, the time constants obtained from the cutoff frequency reflect the length of a burst of openings (Fig. 1C).

Non-stationary variance analysis of time-varying currents

All electrical signals that neurophysiologists study are time varying (for example, synaptic currents and action potentials), many of which never reach steady state for long enough to apply stationary variance analysis. Moreover, experimental recording of responses of the underlying channels is often difficult because desensitization reduces the signal at steady state to a level where analysis is difficult and interpretation complex. A useful but artificial level of activity can be maintained for some ion channels activated with non-natural agonists or subject to treatments that remove desensitization. However, these are

largely unsatisfying solutions. Sigworth¹¹ was the first to describe the adaptation of noise analysis to random current fluctuations that arise from the stochastic properties of Na^+ channels that undergo rapid inactivation, and this approach is generally valid for all time-varying, channel-mediated currents in a model-independent manner. By recording many responses, it is possible to estimate the true response time course (broken line in Fig. 2A). Subtracting this estimate from individual current responses (unbroken line in Fig. 2A) isolates random current fluctuations that result from stochastic properties of ion channels, and these current fluctuations can be analyzed using a modification of Eqn 1 in which the variance and current are time dependent (Fig. 2B). The covariance and power spectrum^{15–18} of current fluctuations isolated from time-varying responses can also (with some modifications) be calculated if sufficiently long responses exist that allow evaluation of the low-frequency spectral components. From these analyses, the channel conductance $p(\text{open})$ and open time or burst length can be estimated. As described above, these estimates can be complicated by the presence of sublevels, but, unless just one channel exists in the patch, single channel analysis is also complex for channels that rapidly open with a high $p(\text{open})$ to multiple conductance levels and rapidly close (Fig. 3).

Non-stationary variance methods have seen a resurgence of interest as investigators study signals that arise under more physiological conditions. Although healthy skepticism exists among researchers not familiar with these methods, the potential pitfalls of this approach have been carefully considered. When analysis is complicated by response-amplitude run-down, local averaging can minimize non-stationarity of the response^{11,12,14}. Furthermore, several investigators have discussed criteria for rejecting records with artifactual variance, alignment of the response waveform with individual responses, the contribution of other noise sources and errors inherent in the approach and the effects of filtering^{12,14,15}. All of these studies show that non-stationary variance analysis can be reliable when applied to high quality data, yielding reasonable (<10%) confidence intervals for i and N when $p(\text{open}) > 0.4$. Non-stationary variance analysis has also been adapted to estimate single channel properties from synaptic currents (Box 1). Finally, it is noteworthy that Sigworth¹¹, on the basis of non-stationary noise analysis, suggested that the fluctuation in axon excitability originally studied by Verveen and Derksen¹ might reflect random Na^+ channel gating. Thus, the two topics under consideration here, membrane-current noise as a tool and noise in information processing, have important historical and conceptual links.

Present uses of noise analysis of membrane currents

There is no question that the various interpretative ambiguities discussed above render noise analysis less useful than single-channel analysis. However, noise analysis still has a place in the analysis of membrane currents, and remains the only recourse in situations where direct recording from the channels of interest is impossible, or the single-channel properties render meaningful analysis of unitary currents hopeless. We consider four such examples.

(1) Low-conductance channels or transporter-linked conductances can only be studied with noise analysis:

glutamate receptors with exceedingly low single-channel conductances (100s of fS) have been studied for a decade using variance analysis¹³. Even at large transmembrane voltages, the predicted unitary currents from such channels are below the limit of detection for single-channel studies. In addition, some electrogenic neurotransmitter transport proteins generate noise in excess of that predicted from the transport velocity, and this noise might reflect their channel-like nature or an associated ion-conductance pathway^{19,20}. Without a quantum leap forward in recording resolution, the study of these low-conductance pathways will only be possible using noise analysis.

(2) Many channels are inaccessible to the patch pipette: excised membrane patches can readily be pulled from cell soma and dendrites. However, synaptic channels are localized away from these regions in close association with presynaptic terminals, and therefore cannot be studied in excised or cell attached membrane patches. Consequently, attempts to study single-channel properties must either rely on electrotonically compact cells in which synaptic single-channel currents are discernible in the whole cell configuration, or on noise analysis (Box 1).

(3) The kinetic properties of some channels complicate single-channel analysis: for example, the endogenous agonist glutamate activates some of its receptors in less than 100 μ s, and continued activation leads to rapid (5–20 ms) desensitization. Because these receptors open to multiple conductance levels, it is hard to distinguish between a single-channel opening and a large conductance level, or between multiple channels opening simultaneously and smaller conductance levels (Fig. 3). Furthermore, synaptic activation of these receptors probably occurs with a high $p(\text{open})$, increasing the likelihood that multiple channels, if present in the patch, will open simultaneously in experiments designed to mimic physiological conditions. In this situation, non-stationary noise analysis can be used to estimate the weighted mean channel conductance and $p(\text{open})$ for the non-desensitized receptor, provided that subconductance levels are minor or their amplitudes are known. Similar information can only be obtained from single-channel recordings if one active channel resides in the patch, although if transmitter concentration is low for much of the postsynaptic current, the time constants describing open and shut durations measured at low agonist concentration might approximate those of synaptically activated channels.

(4) The variance of open-channel current fluctuations contains useful information: open-channel noise has been analyzed using spectral methods similar to those described above^{21–23}, as well as evaluation of the amplitude histograms constructed from the open current fluctuations^{24,25}. Evaluations of the

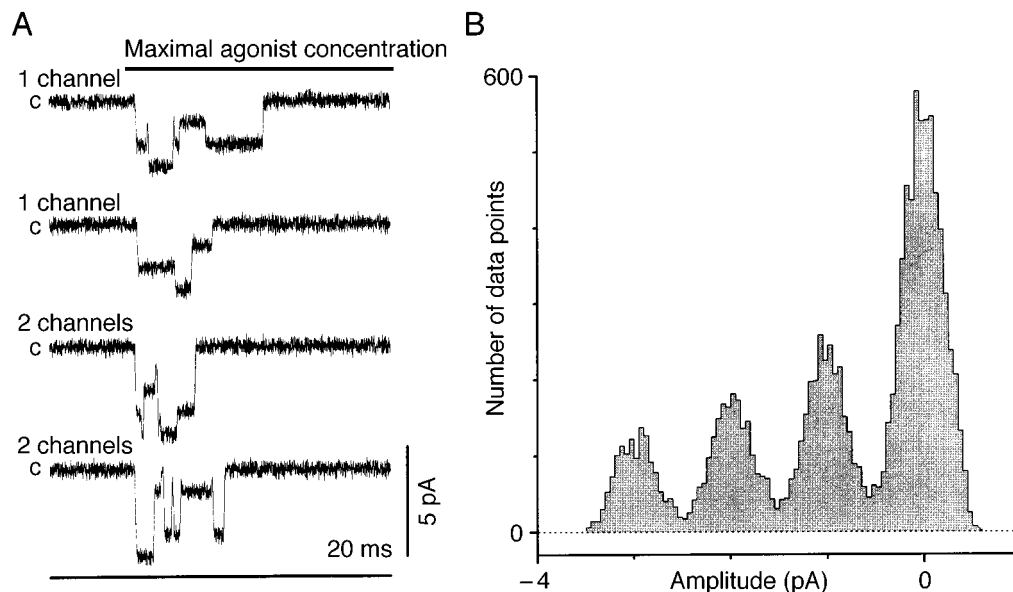


Fig. 3. (A) The traces show simulated responses for a channel that exhibits three conductance levels: 10, 20 and 30 pS, where $i_{\text{RMS}}=0.2 \text{ pA}^2$ with a 5 kHz filter and a 10 μ s interval). When only a single channel is active in the patch (upper two traces), interpretation of a histogram constructed from all the data points, (B), which conveys amplitudes and relative contribution of the channel substates, is straightforward. By contrast, the lower two traces in (A) are simulated responses of two channels in a patch, and illustrate how difficult it is to know whether any given current level (other than the minimal) arises from one or a greater number of open channels. The ambiguity associated with the analysis of several rapidly activating and desensitizing high- $p(\text{open})$ channels with multiple conductance levels complicates the usually clear-cut results of single-channel analysis. Abbreviation: c, the closed state.

nature of the excess open-channel noise can be used to draw inferences concerning channel subconductance levels, ion-permeation properties, or fast channel block. The high frequency of channel blockages by some permeating ions or other molecules and the small differences between sublevel amplitudes confounds attempts to study them as individual single-channel transitions.

Noise in biological systems

Noise analysis is a useful tool because noise is a manifestation of the fundamental character of a specific process: channel gating. However, rather than being a neatly contained display, noise spills into the system, affecting the behavior of other components. For example, when a voltage-dependent ion channel undergoes random transitions between open and closed states the result is a fluctuating current. This current induces a voltage noise that is sensed not only by this channel, but by other voltage-dependent channels. In an isopotential cell, individual channels sense the undiminished contribution of random fluctuations from all active channels. Furthermore, synaptic transmission, one of the basic staples of neuronal processing, is an intrinsically 'noisy' process. The stochastic nature of synaptic transmission is exemplified by the fluctuations in both the number of quanta released by a nerve terminal in response to the same stimulus and the number of postsynaptic receptors activated by transmitter release (Box 1).

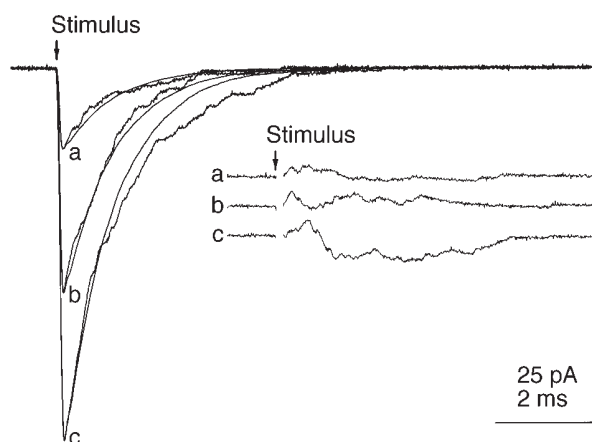
The CNS is, therefore, a noisy environment. Is this noise merely a consequence of the underlying stochastic processes or does noise play an active (positive or otherwise) role in information processing? The notion that noise could play a constructive role was developed simultaneously with the advances on ion-channel function described in the first part of this

Box 1. Variance analysis of synaptic currents

Without a technological breakthrough, it will not be possible to record unitary currents through postsynaptic channels that do not possess large conductances and long open times, two properties that make it possible to see individual transitions in the decay of the postsynaptic currents (PSCs) in electrotonically compact neurons^a. Therefore, the only way in which synaptic channel properties such as the unitary current, burst length and the open probability of the channel or $p(\text{open})$ can be estimated at many synapses is by variance analysis of PSCs. Several groups have adapted non-stationary variance analysis to PSCs, which arise from channels whose $p(\text{open})$ varies with time. However, non-stationary variance analysis of PSCs is complex because current amplitude varies not only as a result of random channel gating^b, but also with variations in the transmitter release, the temporal and spatial transmitter concentration profile^c, and the numbers of channels in the postsynaptic membranes (when PSCs arise from different release sites). The key to successful application of non-stationary variance analysis to PSCs with a variable number of open channels at the peak is the isolation of fluctuations that are a result of stochastic channel gating from those that arise from other sources. Two approaches have been used to scale an estimate of the true PSC waveform to individual PSCs (for example, noisy traces in the Fig.): least squares fitting of the response waveform to each individual current^d and scaling the peak of the waveform directly to the peak of each response^{e,f}. The scaled waveform (smooth traces in the Fig.) is then subtracted from the PSC to isolate current fluctuations (Fig. inset) that can be analyzed using:

$$\sigma(t)^2 = i I(t) - [I(t)^2/N]$$

Although these methods eliminate information about $p(\text{open})$ and the number of channels, the current–variance relationship obtained appears parabolic when few receptors open for the first time after the peak (that is, latency to first opening and transmitter lifetime in the left are brief) or when receptors possess a high $p(\text{open})$ at



article. Several strategies have been conceived to use noise in this fashion. For instance, a neuron can employ input correlations to process information. It can be shown that random, spontaneous activity can facilitate this task²⁶. The presence of noise affects the behavior of relatively simple systems, such as motoneurons, whose discharge is a function of the weighted contribution of multiple inputs. It has recently been shown that synaptic noise can alter the

the peak response^{e,f,g} (see also Refs h,i for analysis of PSCs without peak scaling).

Analysis of simulated synaptic currents suggest that methods for isolating stochastic current fluctuations can be successful, provided that the PSC waveform is invariant from event to event, the electrotonic structure of the neuron is compact, neurotransmitter release is synchronous, transmitter concentration is nearly uniform for synaptic receptors and there is no correlation between unitary current and PSC amplitude. Furthermore, even when the parabola is skewed by post-peak channel openings, meaningful estimates of the unitary current can still be obtained by analyzing the variance of the tail of the PSC (Refs d–f). Variance analysis of spontaneous miniature PSCs, which presumably arise from the release of a single transmitter packet, can circumvent problems associated with asynchrony of transmitter release. In addition, correlations between unitary current and PSC amplitude can be tested by analyzing subsets of large and small PSCs, or by normalizing the variance of each response to the peak amplitude^{e,i}. If there is no correlation between response amplitude and the underlying channel conductance, normalized current–variance relationships can be pooled between different cells, and provide estimates of i identical to the equation above.

In several studies, the unitary current estimated from non-stationary variance analysis of PSCs compares well with single-channel currents, either resolved in the tail of the PSC or recorded from somatic excised patches^{a,d–i,k,l}. Determination of synaptic-channel conductance can, together with the miniature PSC peak amplitude, be used to estimate the minimal number of receptors that open in response to release of a single transmitter packet^{e,f}. Results from this approach and estimates of relatively high $p(\text{open})$ for central synaptic receptors^{h,i} support the idea that a variable^g and an often surprisingly low number of receptors (6–100) exist at some active sites.

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patterns of motoneuron firing, perhaps through negative co-operativity between synapses²⁷. However, it is in the simplest systems that a positive role for noise is becoming particularly evident. This thinking has been driven by the discovery of stochastic resonance (SR) in non-linear systems (Box 2). For example, for biological systems that exhibit a threshold, such as spike-generating neurons, subthreshold signals have no effect on the output of the system. In other words, all information

Box 2. Stochastic resonance

Classically, stochastic resonance (SR) is described as a phenomenon where the response of a non-linear system to a weak, periodic stimulus is optimized by the presence of an optimal level of noise^{a,b}. The simplest, and one of the main types of SR is observed for a simple threshold model. In the example shown (Fig.) the input to the system consists of a 3 mV, 50 Hz sine wave (labeled 'signal'), whereas the output of the system consists of a 1 mV, 1 ms pulse that is triggered every time the signal plus noise increases to or beyond the 5 mV threshold. Although a subthreshold (3 mV) stimulus is unable to affect the output of the system, the addition of noise to the signal leads to threshold crossings that are correlated with the stimulus. The effects of noise on this system can be quantified by obtaining the power spectrum of the output pulse series (lower panel), with a peak at the stimulus frequency indicating the system's output. The signal-to-noise ratio (SNR) can be defined as $10 \log_{10}(S/N)$, where S is the integral of the peak at the stimulus frequency and N is the amplitude of the background noise at the signal frequency. The latter can be easily obtained in the absence of a stimulus, or by measuring the background noise at

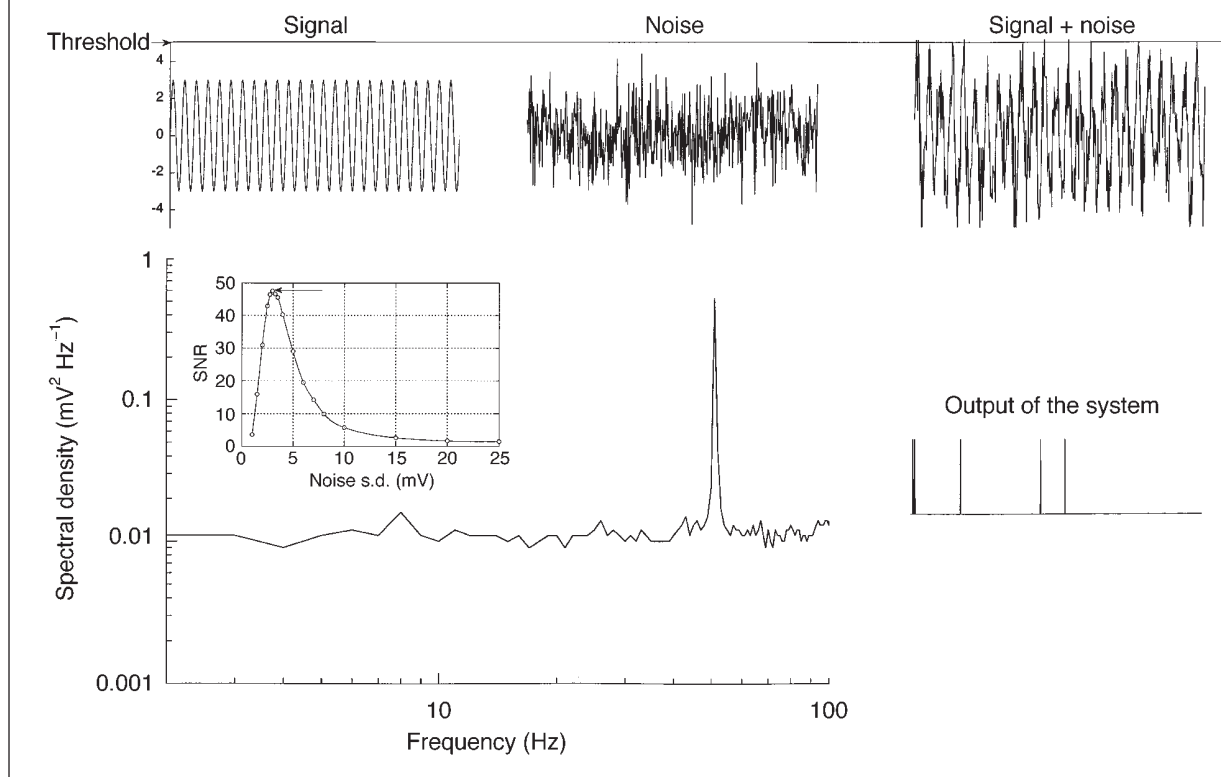
locations adjacent to the peak. The hallmark of SR is the existence of a certain non-zero noise level at which the SNR is optimum (inset). Typically:

$$\text{SNR} \propto \left(\frac{\epsilon \Delta U}{D} \right)^2 \epsilon(-\Delta U / D)$$

where ϵ is the strength of the input signal, ΔU is the height of an energy barrier (or the threshold height) and D is the noise strength^a. For a threshold system, and given a subthreshold signal, increasing noise produces a rapid rise in SNR, followed by a decline, as noise overwhelms SR. The level of noise used to produce the traces shown in the figure was the optimum level (see arrow in the inset). Note that with this optimum level there are few points above threshold, but crossings are highly correlated with the signal peaks.

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present in the signal is lost. It is now evident that given the existence of a threshold, noise arising from different sources can enhance signal detection (Box 2) by allowing the system to reach threshold. It might be argued that such a strategy would bypass the threshold as a safety device against 'false positives', for example, a cell with a 5 mV threshold might have been specifically designed to avoid detecting a 3 mV stimulus. However, for some sensory systems, such false positives do not exist. For example, hair cells, the mechanosensory receptors of the vestibular and auditory systems, respond in a graded fashion to the smallest motion. A signal too weak to trigger afferent firing is essentially lost. As shown below, SR could improve sensory systems in several ways.

SR has been described in the past as a nonlinear cooperative effect by virtue of which the response of a system to a weak periodic signal is enhanced by the addition of an optimal amount of noise. Three caveats about this definition help illustrate how widespread this effect is.

(1) The signal need not have a single frequency component: in addition to simple threshold and bistable potential systems, SR is also seen in the reset-and-fire excitable system. This system, much like a neuron, integrates a stimulus until a threshold is reached. At this point the system 'fires' and resets. This suggests that axonal transmission of information could be enhanced by noise contrary to the classical theory that states that the capacity of an information channel

increases monotonically with the signal-to-noise ratio (SNR)²⁸. Indeed, it has been shown that noise can enhance the quality of transmission in the nervous system^{29,30}. More recent experiments in the cricket cercal sensory system have shown that the transmission of signals by the sensory *cercal*, measured in bits per action potential, is also enhanced by noise³¹. Furthermore, these signals were relatively broad banded (5–400 Hz), indicating that SR can exist across the spectrum of frequencies commonly employed by axons.

(2) The signal need not be periodic: although periodic signals are commonly used experimentally, sensory systems are rarely subject to a pure periodic stimulus. However, recent experiments on rat cutaneous mechanoreceptors indicate that noise can enhance the transmission of aperiodic stimuli, again suggesting a role for noise in enhancing sensory transmission of biologically relevant signals³².

(3) Noise need not be optimized: for the relatively simple system portrayed in Box 2 there is an optimum noise level. Below this ideal level the system is not optimized, whereas beyond it the SNR is degraded. However, such dependence is not an obligatory feature for all systems that exhibit SR. A recent report by Collins *et al.* shows that a summing network of identical model neurons is not subject to this limitation³³. As the number of constitutive elements in the network increases, the steepness with which the SNR decreases as noise surpasses the optimum level, is progressively reduced. These results indicate that for a relatively large network (more than 1000 elements) a certain fixed amount of noise can be added to the constitutive elements in order to optimize the performance of the network. This added noise has to be 'sufficient', that is, there is a minimum level that has to be added, but no 'tuning' is required. Although this noise level does not guarantee optimal performance from individual elements it does ensure nearly optimal responses from the network. The behavior of model networks is not necessarily indicative of CNS organization. However, the work of Collins and his colleagues has led to speculation about the possibility of SR in the brain. It should be noted that although white noise is often used to model SR, colored noise (Fig. 1C) can effectively produce similar behaviors. An example is the noise generated by the random gating of ion channels. This noise, rather than being white, has spectral characteristics that are determined by the transition rates between different states (Fig. 1).

Although a simple threshold system is often used to introduce SR, the existence of such a threshold is not a requirement, as shown for the voltage-dependent ion channel alamethicin by Bezrukov and Vodyanov³⁴. The behavior of alamethicin is similar to that of other ligand- and voltage-dependent ion channels, that is, it does not show a clear threshold. Instead, the probability that the channel will be open can be continuously biased by its natural stimulus. Recently these same authors have clarified the theoretical basis for SR in systems without a threshold³⁵. In this paper the authors model the behavior of such a system as a Poisson process with a rate of random transitions that depends exponentially on the stimulus amplitude. This kind of behavior is typical of many biological processes, such as gating of ion channels, which open randomly with a rate that depends, for example, expo-

nentially on voltage. Similarly, mechano-electrical transduction channels in hair cells open randomly with a rate that depends exponentially on hair bundle displacement. Bypassing a discussion of the mechanistic origins of the Poisson process, Bezrukov and Vodyanov³⁵ show that such a system exhibits SR. The presence of SR in these systems raises the possibility of similar effects for ion channels in the CNS, and thus for the behavior of an enormous range of processes from sensory transduction, to signal activation of voltage- and ligand-gated ion channels and neurotransmitter transporters at neuronal synapses, to signal integration at neuronal somata and dendritic processes, to the behavior and noise dependence of neural networks.

In summary, SR might be a general strategy employed by the CNS for the improved detection of weak signals. However, the effects of SR in sensory processing might extend past an improvement in signal detection. As information flows towards progressively more central relay stations, it is handled by systems that might exhibit SR, resulting in improved information processing. This enhancement might start to take place at the earliest stages of processing, as recently suggested by the enhanced vowel coding obtained with the addition of noise to cochlear implants³⁶.

Outlook

Noise analysis has been an important tool during the formative years of the study of ion channels. Although single-channel recording has replaced noise analysis for the most part, it is still useful for analyzing channel function in certain situations. Moreover, it is likely to remain so until technological advances enable routine recording of patches with a single channel, individual postsynaptic or low conductance channels and closely spaced subconductance levels. Moreover, the appreciation of random processes that noise analysis has brought to neuroscience is far from trivial. Most researchers are familiar with the probabilistic nature of membrane conductances, and this familiarity makes fertile ground on which to pose questions about the role of noise in information processing. Indeed, it seems likely that stochastic resonance and noise contribute to information processing throughout the nervous system on a scale that could not have been predicted from original studies of variable axonal firing¹.

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LETTERS TO THE EDITOR

Schizophrenia as failure of hemispheric dominance for language

In his Viewpoint article, Crow stated that the prevalence, incidence and clinical features of schizophrenia are remarkably similar across cultures¹. However, there is evidence that schizophrenic symptomatology is markedly different between countries, and that, in some, the incidence of the disorder has increased by as much as 45% in a short period of time². Crow indicated that a deficit in lateralization, particularly of the neural control of language, causes the illness¹; this is in contrast with the suggestion that there are multiple and distributed neural controls of schizophrenic symptomatology³. In addition, Crow suggested that a 'genetic factor' controls the development of schizophrenia and therefore, on his hypothesis, language¹. This contrasts with the suggestion that there are redundant genetic controls of the brain mechanisms of language⁴ and of the liability to schizophrenia⁵. If all of this is correct, we must conclude that schizophrenia has redundant external, neural and genetic controls. There are probably many, but let us conservatively assume there are four of each. This would allow for $4! \times 4! \times 4! = 13\ 824$ combinations between genes, brain functions and schizophrenic symptoms. Does not this make the search for a neurobiology of schizophrenia an impossible project?

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I am unhappy about Crow's claims that: (1) lateralization of the human brain is its most specific feature; (2) all our heteromodal association areas have evolved via language lateralization; (3) language is what separates us from early hominids; (4) hemispheric specialization is how language has evolved; and (5) language, not intelligence, is what has been selected for in our evolution. Laterality is pervasive throughout the animal kingdom^{1,2}; although associated with language, it might not be an essential component, and many other factors, including Machiavellian intelligence³, might have been important for selection.

Not all stutterers, developmental dysphasics or dyslexics are abnormally lateralized, nor does this inevitably lead to such syndromes or psychosis, nor indeed do such language dysfunctions and psychosis correlate or occur as co-morbidities. In addition to the left hemisphere, the right hemisphere plays a major role in the connotative and pragmatic aspects of language⁴. The phonological and syntactic aspects of language might even have been 'attracted' to the left hemisphere because of a prior underlying commitment to analytic, sequential, time-dependent (or even praxic) functions⁵, or simply because right-hemisphere processing space was already pre-empted for spatial or emotional processing¹.

I query whether it is language that is the most lateralized, has evolved the most recently and develops over the longest ontogenetic time course. Praxis is no less lateralized than language; the latter probably has a very long evolutionary history, and there are surely many other cognitive and social functions that take just as long to develop as language, which becomes well established in the first few years of life.

Although delayed or incomplete lateralization might indeed be associated with the risk of developing schizophrenia (or language dysfunction), there is not necessarily a causal connection; delayed or incomplete lateralization might merely be epiphenomenal to other underlying disturbances. If schizophrenia is due to a breakdown of interhemispheric, transcallosal inhibition, such that the left hemisphere perceives right-hemisphere influences as 'outside voices', there should also be other, motor consequences such as overflow, mirror movements or alien sign⁶ in schizophrenia. Conversely, there can be no condition where the hemispheres function more independently than in congenital callosal syndrome⁷, but there is no evidence there of psychosis.

The claim that increased ventricular space and reduced cortical mass in schizophrenia are due to failures to develop asymmetry, and that schizophrenia is largely independent of epigenetic, environmental influences fails to recognize the literature on seasonality of birth⁸ and possible febrile illnesses in the mother during critical stages of neurogenesis; such factors could act upon a genetic susceptibility. Abnormalities of lateralization, callosal morphology and cortical and ventricular development could then be epiphenomena of psychosis.

I doubt that the rapid increase in our allometric brain to body weight ratio is due to progressive lateralization. Notably, I query such pervasive specialization, and suggest that our allometric advantages