SYNAPTIC “NOISE”: EXPERIMENTS, COMPUTATIONAL CONSEQUENCES AND METHODS TO ANALYZE EXPERIMENTAL DATA

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Synaptic “noise”

Abstract

In the cerebral cortex of awake animals, neurons are subject to tremendous fluctuating activity, mostly of synaptic origin, termed “synaptic noise”. Synaptic noise is the dominant source of membrane potential fluctuations in neurons and can have a strong influence on their integrative properties. We review here the experimental measurements of synaptic noise, and its modeling by conductance-based stochastic processes. We then review the consequences of synaptic noise on neuronal integrative properties, as predicted by computational models and investigated experimentally using the dynamic-clamp. We also review analysis methods such as spike-triggered average or conductance analysis, which are derived from the modeling of synaptic noise by stochastic processes. These different approaches aim at understanding the integrative properties of neocortical neurons in the intact brain.

9.1 Introduction

The cerebral cortex is characterized by an extremely dense connectivity, with each pyramidal neuron receiving between 5000 and 60000 synaptic contacts. A large part of this connectivity originates from the cortex itself (Braitenberg and Schüz, 1998, DeFelipe and Farinas, 1992). In awake animals, neurons in different cortical structures display high spontaneous firing rates (Evarts, 1964, Steriade and McCarley, 1990). As a consequence, many synaptic inputs are simultaneously active onto cortical neurons in intact networks. Indeed, intracellular recordings in awake animals reveal that cortical neurons are subjected to an intense synaptic bombardment and, as a result, are depolarized and have a low input resistance (Baranyi, Szente and Woody, 1993, Matsumura, Cope and Fetz, 1988, Steriade, Timofeev and Grenier, 2001) compared to brain slices kept in vitro. This activity is also responsible for a considerable amount of subthreshold fluctuations, called “synaptic noise”. Together these properties are described as the “high-conductance state” of cortical neurons. How such high-conductance and high-noise conditions affect the integrative properties of neurons remains an intense subject of research (reviewed in (Destexhe, 2007, Destexhe, Rudolph, Paré et al., 2003)).

In this chapter, we give an overview of the experimental measurements of synaptic noise in cortical neurons in vivo. We next review computational models with which to explore the impact of synaptic noise on integrative properties, and to determine what sort of computational advantages can be conferred by noise. Finally, we review experimental methods derived from the stochastic modeling of synaptic noise, and discuss how such methods could be tested experimentally.

9.2 Experimental characterization of synaptic noise

9.2.1 The noisy subthreshold activity in different brain states

The intracellular recording shown in Fig. 9.1A (Awake) shows the membrane potential ($V_m$) activity of a cortical neuron in an awake cat. The $V_m$ activity is characterized by a considerable amount of synaptic activity and fluctuations which
give rise to irregular firing. Although this fact is well known, it was only characterized relatively recently. Most of the data have been obtained in intracellular recordings under anesthesia, and in some cases, in awake or naturally sleeping animals (reviewed in (Destexhe, Rudolph, Paré et al., 2003)). In awake animals, the cerebral cortex (and more generally the entire brain) displays an “activated” state, with distinct characteristics compared to other states like slow-wave sleep or anesthesia. These characteristics include a low-amplitude “desynchronized” electroencephalogram (EEG), a depolarized $V_m$ and irregular firing activity, all visible in Fig. 9.1A (Awake). During slow-wave sleep, the EEG and $V_m$ activity follow low-frequency rhythms (Fig. 9.1A, Slow-Wave Sleep). The most prominent rhythm consists of slow-wave complexes in the EEG, which are paralleled with up/down-state dynamics in the $V_m$. During the up-state (grey bars in Fig. 9.1A), the $V_m$ is depolarized and the activity is similar to wakefulness; during the down-state, all cortical neurons are hyperpolarized and do not fire. Several anesthetics, such as urethane or ketamine-xylazine, induce EEG and $V_m$ dynamics very similar to slow-wave sleep. For instance, ketamine-xylazine anesthesia induces up/down states very similar to sleep (grey bars Fig. 9.1B). For recent reviews on EEG and $V_m$ dynamics during activated and sleep states, see (Steriade, 2001, Steriade, 2003, McCormick and Bal, 1997, Steriade and McCarley, 1990).

One of the main interesting aspects of up/down states is that there is good evidence that the up-states follow dynamics very close to the activated states of the brain (for a recent review, see (Destexhe, Hughes, Rudolph and Crunelli, 2007)). At the level of EEG and intracellular activities, the dynamics seen during up-states are extremely similar to that during wakefulness. An illustrative example of this similarity is that electrical stimulation of the brain stem (pedonculo-pontine tegmentum, or PPT) can transform the up/down-state dynamics into the typical desynchronized EEG of activated states (Fig. 9.1B). Following the PPT stimulation, this artificial activated state appears as a “prolonged” up-state (see (Steriade, Amzica and Nunez, 1993, Rudolph and Destexhe, 2005)). Thus, it seems that the up-states constitute a relatively good approximation of the network state during activated states. It is important to stress that these states are close, but not identical, as shown for example by conductance measurements (see (Destexhe, Hughes, Rudolph and Crunelli, 2007)).

Other types of anesthetics, such as barbiturates, do not induce dynamics comparable to either activated or slow-wave sleep states but rather depress cortical activity and induce an EEG dominated by slow waves (Fig. 9.1C). In this case, the $V_m$ is hyperpolarized, and rarely makes excursions to depolarized values. The most depressed state is obtained in vitro (Fig. 9.1D), where the $V_m$ is at rest with rare synaptic events (Fig. 9.1D, inset). In some cases, manipulations are possible to excite cortical activity, resulting in the spontaneous generation of up/down-state dynamics in vitro (Sanchez-Vives and McCormick, 2000).
Fig. 9.1. Membrane potential activity during different states of cerebral cortex. A. Intracellular recordings and electroencephalogram (EEG) in the association cortex of cats (area 5-7, see scheme), during the waking state (left) and during slow-wave sleep (right). The activity during sleep consists of up- and down-states (up-states indicated by grey bars; modified from (Steriade, Timofeev and Grenier, 2001)). B. Activity during ketamine-xylazine anesthesia. The spontaneous activity (up and down states) switches to a prolonged up-state with desynchronized EEG after stimulation of the PPT (vertical bar; grey bars indicate up-states; modified from (Rudolph and Destexhe, 2005)). C. Activity during barbiturate anesthesia. The membrane is mostly hyperpolarized, with occasional depolarizations. D. Activity in cortical slices (In vitro). Synaptic activity is diminished and mostly consists of unitary synaptic potentials (see inset at higher time resolution; C-D modified from (Pare, Shink, Gaudreau, Destexhe and Lang, 1998)).

9.2.2 Conductance measurements
The first way to characterize synaptic noise is to build \( V_m \) distributions, as shown in Fig. 9.2A and B. From such distributions at different levels of DC injection, one can grossly evaluate the conductance underlying each phase of the oscillation. In ketamine-xylazine anesthesia (Fig. 9.2A), the \( V_m \) distributions
are bimodal, with left and right peaks corresponding to the down- and up-states, respectively. By injecting different levels of current, it is apparent that the current has a much more powerful effect in shifting the down-states, whereas it produces only a minor shift of the up-states (compare different curves in Fig. 9.2A). In other words, the up-state has a much larger conductance compared to the down-state. The behavior during barbiturate anesthesia (Fig. 9.2B) reminds one of the down-state, in agreement with the recordings shown in Fig. 9.1B-C. These measurements (Pare, Shink, Gaudreau, Destexhe and Lang, 1998) constitute a first indication that the up-states correspond to a high-conductance state. The same results were obtained with purely subthreshold activity, showing that they are not due to the conductances of action potentials.

A second, more direct, measurement was obtained by comparing the intracellular recording during up-states and after total suppression of network activity using TTX (Fig. 9.2C; Pare, Shink, Gaudreau, Destexhe and Lang, 1998)). Because TTX blocks all sodium channels, it completely suppresses all action-potential dependent activity and reveals the resting state of the neuron. Input resistance ($R_{in}$) measurements revealed that taking the up-states of ketamine-xylazine anesthesia as reference, these active states have about 5 times more synaptic conductance compared to the resting state of the cell (Fig. 9.2C; Destexhe and Pare, 1999, Pare, Shink, Gaudreau, Destexhe and Lang, 1998). These results are not affected by the $V_m$ level nor by spiking activity (identical results are obtained at hyperpolarized, subthreshold levels) and $R_{in}$ measurements correspond to the linear portion of the I-V curve, suggesting little or no contamination by intrinsic voltage-dependent currents (Destexhe and Pare, 1999; see also discussion in Monier, Fournier and Frégna, 2008).

Measurements have also been obtained during active states in vivo in other preparations, usually by comparing up and down-states under various anesthetics such as ketamine-xylazine or urethane. Such estimates are very variable, ranging from up to several-fold smaller $R_{in}$ in up-states (Contreras, Timofeev and Steriade, 1996, Leger, Stern, Aertsen and Heck, 2005, Pare, Shink, Gaudreau, Destexhe and Lang, 1998, Petersen, Hahn, Mehta, Grinvald and Sakmann, 2003), to nearly identical $R_{in}$ between up- and down-states or even larger $R_{in}$ in up-states (Metherate and Ashe, 1993, Waters and Helmchen, 2006, Zou, Rudolph, Roy, Sanchez-Vives, Contreras and Destexhe, 2005).

The latter paradoxical result may be explained by voltage-dependent rectification (Waters and Helmchen, 2006) or by the presence of potassium currents in down-states (Zou, Rudolph, Roy, Sanchez-Vives, Contreras and Destexhe, 2005). Consistent with the latter, cesium-filled electrodes have negligible effects on the up-state, but largely abolish the hyperpolarization during the down-states (Timofeev, Grenier and Steriade, 2001). Moreover, the $R_{in}$ of the down-state differs from that of the resting state (after TTX) by about two-fold (Pare, Shink, Gaudreau, Destexhe and Lang, 1998).

It is, thus, clear that at least the down-state is very different from the true resting state of the neuron. Finally, conductance measurements in awake and naturally sleeping animals have revealed a wide diversity between cells in cat cortex (Rudolph, Pospischil, Timofeev and Destexhe, 2007), ranging from large
FIG. 9.2. Conductance measurements in different cortical states.
A. Different levels of current injection during ketamine-xylazine anesthesia reveal that the up-states (right peaks) have a much larger overall conductance compared to down-states (left peaks). B. During barbiturate anesthesia, the behavior was similar to down-states. C. Quantification of the conductance state of the membrane in up-states by microperfusion of TTX to cortex (see scheme). Hyperpolarizing current pulses were injected during up-states (Before TTX), and later after total suppression of network activity (After TTX), in the same neurons. The overall conductance was about five times lower after TTX for this particular cell (modified from (Pare, Shink, Gaudreau, Destexhe and Lang, 1998)).

(much larger than the leak conductance) to moderate (smaller or equal to the leak) synaptic conductances. On average, the synaptic conductance was estimated to be about three times the resting conductance, with division into about one third excitatory and two thirds inhibitory conductance (Rudolph, Pospischil, Timofeev and Destexhe, 2007). Strong inhibitory conductances were also found in artificially evoked active states using PPT stimulation (Rudolph and Destexhe, 2005), such as that shown in Fig. 9.1B.

In conclusion, the data reviewed here indicate that when the EEG is desynchronized, neocortical neurons are in a “high-conductance state” characterized
by the following features: (i) a large membrane conductance, which corresponds to a three to five-fold decrease in input resistance; (ii) an average membrane potential (around -65 to -60 mV), which is significantly depolarized compared to the natural resting level (-70 to -80 mV); and (iii) large amplitude membrane potential fluctuations ($\sigma_V$ of 2-6 mV), which are at least 10-fold larger than those seen in the absence of network activity. In addition, the data indicate that these characteristics are attributable mostly to network activity, and that inhibitory conductances account for most of the large membrane conductance.

Thus, experiments show that synaptic activity has a tremendous influence on cortical neurons, and this is true for activated states such as wakefulness, so presumably it is an important factor in understanding awake neuronal processing. Computational models are needed to investigate the consequences of synaptic noise on integrative properties, as we review in the next section.

9.3 Computational consequences of synaptic noise

9.3.1 Models of synaptic noise

There is a long tradition of theoretical studies aimed at understanding the impact of noise on the integrative properties of neurons. The notion of a high-conductance state, as well as the fact that neurons could integrate differently in such states, was first suggested by modeling studies. By integrating the sustained synaptic conductance arising from network activity into models, (Barrett, 1975) for motoneurons, and later (Holmes and Woody, 1989) for pyramidal cells, predicted that synaptic activity could have a profound impact on dendritic integration. This theme was then investigated using biophysically and morphologically more precise models in cortex (Bernander, Douglas, Martin and Koch, 1991, Destexhe and Pare, 1999) and cerebellum (De Schutter and Bower, 1994, Rapp, Yarom and Segev, 1992). Such models have predicted a number of computational consequences of background activity and high-conductance states in neurons (see Section 9.3.2 below).

In addition to morphologically precise models, a large number of theoretical studies have designed simplified models to study the effect of noise on neurons. Synaptic activity is usually modeled by a source of current noise in the neuron (Levitan, Segundo, Moore and Perkel, 1968, Tuckwell, 1988), and, thus, the membrane potential is described by a stochastic process. More recently, the background activity has been modeled by fluctuating conductances instead of fluctuating currents (Destexhe, Rudolph, Fellous and Sejnowski, 2001). In this case, the synaptic conductances are stochastic processes, which in turn influence $V_m$ dynamics. The advantage of this representation is that the high-conductance state of the membrane can be specifically reproduced and modulated. The realism and simplicity of those models also enables injection into real neurons in order to recreate high-conductance states artificially (see Section 9.4 below).

Another advantage is that those models are simple enough to allow mathematical treatment. Various mathematical studies of the firing dynamics of neurons with conductance-based inputs were proposed (see for example (Moreno-Bote and Parga, 2005, Muller, Buesing, Schemmel and Meier, 2007, Burkitt, Meffin and Grayden, 2003))
and have consequences on network dynamics with conductance-based inputs (Meffin, Burkitt and Grayden, 2004) (see also (Shelley, McLaughlin, Shapley and Wielaard, 2002)).

We will consider here in more detail the “point-conductance” stochastic process. According to this model, the membrane potential dynamics is described by the following set of equations (Destexhe, Rudolph, Fellous and Sejnowski, 2001):

\[
C \frac{dV}{dt} = -G_L (V - E_L) - g_e (V - E_e) - g_i (V - E_i) + I_{ext}, 
\]

\[
\frac{d g_e (t)}{dt} = -\frac{1}{\tau_e} [g_e (t) - g_{e0}] + \sqrt{\frac{2 \sigma^2_e}{\tau_e}} \xi_e (t), 
\]

\[
\frac{d g_i (t)}{dt} = -\frac{1}{\tau_i} [g_i (t) - g_{i0}] + \sqrt{\frac{2 \sigma^2_i}{\tau_i}} \xi_i (t), 
\]

where \(C\) denotes the membrane capacitance, \(I_{ext}\) a stimulation current, \(G_L\) the leak conductance and \(E_L\) the leak reversal potential. \(g_e (t)\) and \(g_i (t)\) are stochastic excitatory and inhibitory conductances with respective reversal potentials \(E_e\) and \(E_i\). The excitatory synaptic conductance is described by Ornstein-Uhlenbeck (OU) stochastic processes (Eq. 9.2), where \(g_{e0}\) and \(\sigma^2_e\) are, respectively, the mean value and variance of the excitatory conductance, \(\tau_e\) is the excitatory time constant, and \(\xi_e (t)\) is a Gaussian white noise source with zero mean and unit standard deviation. The inhibitory conductance \(g_i (t)\) is described by an equivalent equation (Eq. 9.3) with parameters \(g_{i0}\), \(\sigma^2_i\), \(\tau_i\) and noise source \(\xi_i (t)\).

This conductance-based stochastic process has been extremely useful in studying synaptic noise both in models and real neurons, as will be shown in the next sections.

9.3.2 Impact of synaptic noise on integrative properties

Computational models have predicted several interesting computational consequences of high-conductance states and synaptic noise (reviewed in (Destexhe, 2007, Destexhe, Rudolph, Paré et al., 2003)).

9.3.2.1 Probabilistic responses A first straightforward consequence is that neuronal responses in high-conductance states are fundamentally probabilistic because of the high variability of responses due to the presence of synaptic noise (Fig. 9.3A). In the presence of synaptic noise, it is necessary to use repeated trials for any given response, and calculate the probability of spiking. This variability and the use of probabilities are well-known by in vivo electrophysiologists, who routinely calculate “post-stimulus time histograms” (PSTH) from their data. Integrating the probability of response after the stimulus gives the total probability that a spike is emitted (the total “output” of the neuron; Fig. 9.3B). This measure will be used all through this chapter.

9.3.2.2 Noise-induced enhanced responsiveness A second consequence of high-conductance states is that not only do they transform neurons to probabilis-
tic devices, but they also profoundly change their response properties. The response curve, which is obtained by plotting the total response probability (integrated over time after stimulus) against stimulus amplitude, is all-or-nothing for a deterministic neuron, reflecting the spike threshold (Fig. 9.3B, grey). In this case, the spike can only indicate whether or not the stimulus is larger than the threshold. In the presence of synaptic noise, the response curve is different, it is smooth and spans a whole range of input amplitudes (Fig. 9.3B, black). In this case, the probability of spiking is indicative of the whole range of input amplitudes. In particular, for small-amplitude inputs (those in the physiological range), which are normally subthreshold, the neuron’s response probability is enhanced (Fig. 9.3B, star). This enhanced responsiveness is a very robust feature of neurons in the presence of synaptic background activity (Hö and Destexhe, 2000, Shu, Hasenstaub, Badoual, Bal and McCormick, 2003). A similar phenomenon has also been called “gain modulation” (Chance, Abbott and Reyes, 2002), reflecting the fact that the slope of the response curve is modulated by synaptic noise.

With models, it is possible to decompose synaptic noise into its conductance component and the “noise” component. The conductance alone shifts the response curve (rightward arrow in Fig. 9.3B), while the noise component alone modulates the slope (gain) of the response curve (Hö and Destexhe, 2000, Mitchell and Silver, 2003, Prescott and De Koninck, 2003, Shu, Hasenstaub, Badoual, Bal and McCormick, 2003, Chance, Abbott and Reyes, 2002). It is important to note that the type of modulation by noise will depend strongly on the intrinsic properties of the neurons. An inverse gain modulation can be observed (Fellous, Rudolph, Destexhe and Sejnowski, 2003) and may be explained by the presence of potassium conductances (Higgs, Slee and Spain, 2006). Similarly, the dual response (burst vs. single-spike) of thalamic relay neurons is also strongly affected by the presence of synaptic noise and the two modes may no longer be distinguishable (Wolfart, Debay, Le Masson, Destexhe and Bal, 2005) (see Section 9.4 below).

The phenomenon of enhanced responsiveness is similar to that of stochastic resonance, which has been thoroughly studied by physicists (reviewed in (Wiesenfeld and Moss, 1995, Gammaitoni, Hönggi, Jung and Marchesoni, 1998); see chapter 4 in this volume). Stochastic resonance (SR) is a noise-induced enhancement of the signal-to-noise ratio in nonlinear systems. It usually appears as a peak of the signal-to-noise ratio as a function of noise amplitude, thus the system appears to “resonate” or to respond optimally for an intermediate but non-vanishing amount of noise. While neurons can also show such behavior if subject to noise (Levin and Miller, 1996, Stacey and Durand, 2000), the situation is more complex than for classic stochastic resonance phenomena, because in neurons the noise source is also a conductance source, and conductances have an additional shunting effect (see details in (Rudolph and Destexhe, 2001b)). As we will see below, this modulation of neuronal responsiveness by noise is the basis for the explanation of other neuronal response properties.
Fig. 9.3. Increased responsiveness in the presence of synaptic noise.

A. In the presence of synaptic noise, the response to additional inputs is highly variable, and spikes are evoked at different latencies at each trial (40 trials are shown for two different input amplitudes). B. Modulation of the response curve. The response curve (probability of evoking spikes as a function of input amplitude) is all-or-nothing in quiescent conditions (grey). Decomposing synaptic activity into “conductance” and “noise” components shows that conductance shifts the curve rightward (grey dashed), while the noise changes its slope (gain modulation; black). The response of the neuron is a combination of these effects, showing enhanced responsiveness (star) for otherwise subthreshold input regime (modified from (Hô and Destexhe, 2000)).
9.3.2.3 Equalization of synaptic efficacies A third consequence of synaptic noise states is that it may fundamentally change dendritic integration properties, as illustrated in Fig. 9.4. An inherent property of dendrites and other cable structures is voltage attenuation. This is true in particular for pyramidal neurons; synaptic inputs can experience strong attenuation in the neuron’s resting state (Fig. 9.4A, left). If the high-conductance state of the membrane is integrated as a static conductance component (i.e., increasing the leak conductance of the membrane), the attenuation is much more severe (Fig. 9.4A, middle): inputs arising at 400 microns or more from the soma are almost totally attenuated, and post-synaptic potentials (PSPs) at the soma are undetectable. This phenomenon is perfectly predictable by cable theory. Remarkably, if the full high-conductance state is simulated, the spiking probability shows a surprisingly low dependence on the location of inputs in dendrites (Fig. 9.4A, right).

How does one explain this equalization of synaptic efficacy? Dendritic excitability, combined with noise, plays a critical role. In quiescent conditions, synaptic inputs arising in distal dendrites can elicit a local dendritic spike, but such a spike is hard to evoke and typically does not propagate well across the dendritic structure (Fig. 9.4B, top). With synaptic noise, as shown above, the behavior is highly variable, and there is a small probability that evoked spikes propagate all the way to the soma (Fig. 9.4B, bottom). The probability that a local dendritic spike propagates to the soma and evokes a somatic spike is inversely proportional to distance (Fig. 9.4C, dark grey). Conversely, the probability that synaptic inputs evoke a local dendritic spike increases with distance (because the local input resistance is higher for distal dendrites; see Fig. 9.4C, light grey). The multiplication of these two probabilities gives the spike probability of synaptic inputs and is necessarily less dependent on location (Fig. 9.4C, black). Thus, according to this “stochastic integrative mode” ( (Rudolph and Destexhe, 2003a)), the neuron could solve one long-standing problem, how to equally integrate inputs situated at different locations in extended dendritic trees. This equalization mechanism depends on both intrinsic properties (dendritic excitability) and the presence of synaptic noise.

9.3.2.4 Sharper temporal processing Another important consequence of synaptic noise is on temporal processing. The large conductance is necessarily associated with a reduced membrane time constant, which is visible in the faster response to injected current (Fig. 9.2C, averaged traces). As proposed more than 30 years ago (Barrett, 1975), this reduced time constant should favor finer temporal discrimination (Bernander, Douglas, Martin and Koch, 1991, Destexhe and Pare, 1999, Holmes and Woody, 1989). In excitable dendrites, small membrane time constants also promote fast-propagating action potentials, resulting in a reduced location-dependence of EPSP timing (Fig. 9.5A; (Rudolph and Destexhe, 2003a)). This property is likely to facilitate the association of synaptic inputs arising at different locations. The neuron also has a superior ability to distinguish and process high-frequency inputs, compared to low-conductance states. This is il-
Fig. 9.4. Location independence of synaptic inputs in high-conductance states. A. Somatic response amplitudes for inputs located at different positions in dendrites. In a quiescent neuron (left), somatic input amplitudes decrease as a function of distance to soma. With a static conductance (middle), this attenuation is stronger. By including both conductance and noise (right), the probability of somatic spikes becomes much less dependent of the position of the input in dendrites. B. Illustration of forward propagating spike in a quiescent neuron (top), and in the presence of background activity (bottom). C. Explanation for location independence based on probabilities of action potential (AP) initiation and propagation (modified from (Rudolph and Destexhe, 2003a)).

Illustrated in Fig. 9.5B, which shows the temporal resolution of a neuron plotted against the input frequency. In quiescent or low-conductance states, neurons can follow inputs (i.e., produce a spike) up to a maximal frequency which is usually around 40-50 Hz (Fig. 9.5B, grey). With synaptic noise, the neuron can lock its response to higher frequencies (up to more than 100 Hz in the example of Fig. 9.5B, black).

Other computational advantages of synaptic noise on temporal processing have been noted by modeling studies. If both excitatory and inhibitory conductances are large during high-conductance states, slight variations of either excitation or inhibition can be very effective in modifying spiking probability. As a
consequence, neurons can reliably detect faint changes in temporal correlation of the random activity of their inputs (Halliday, 2000, Salinas and Sejnowski, 2000, Rudolph and Destexhe, 2001a). This type of response is interesting, because changes in correlation do not change the average conductance nor the average $V_m$, but they appear as changes of the level of fluctuations (variances) of the conductances and of the $V_m$. In this case, neurons respond to a signal which is not carried by the mean activity of conductances, which is an example of a paradigm that cannot be modeled by rate-based models.

High-conductance states also have an impact on the operating mode of cortical neurons. Neurons can operate either as coincidence detectors or as temporal integrators, which determines whether the cortex encodes information by the precise timing of spikes, or by average firing rates. Modeling studies monitored the spike output of neurons subject to a full spectrum of multisynaptic input patterns, from highly coincident to temporally dispersed (Kisley and Gerstein, 1999,
It was found that generally the spike output jitter is less than the input jitter, indicating that neurons tend to synchronize the responses and reduce their temporal dispersion. In high-conductance states, however, the temporal dispersion was found to be nearly identical between input and output (Rudolph and Destexhe, 2003c), suggesting that both operating modes can be used robustly in cortical networks in such states.

9.4 Testing the impact of synaptic noise using dynamic-clamp experiments

A particularly elegant way to evaluate the impact of synaptic noise on neurons is to recreate synaptic noise in a controlled fashion in neurons in brain slices. Because such an experiment requires adding artificial conductances to the neuron, one needs to use an appropriate technique, called dynamic-clamp. This technique was introduced in 1993 independently by two laboratories (Robinson and Kawai, 1993, Sharp, O’Neil, Abbott and Marder, 1993) and is now well-established (Prinz, Abbott and Marder, 2004).

The dynamic-clamp consists of injecting computer-generated conductances into a real neuron through the recording electrode. Because the injected current depends not only on the conductance, but also on voltage \( I = g(V - E) \), one needs to continuously update the current to be injected as a function of the constantly changing voltage. Thus, a computer is required to run the conductance models in real time in order to communicate in a perfectly timed fashion with the recording setup, and in particular the amplifier of the intracellular signal.

The first study to inject synaptic noise in cortical neurons using dynamic-clamp and artificially recreate high-conductance states was proposed in 2001 (Destexhe, Rudolph, Fellous and Sejnowski, 2001), and this was followed by a number of studies which investigated different aspects of high-conductance states using this technique (Fellous, Rudolph, Destexhe and Sejnowski, 2003, Higgs, Slee and Spain, 2006, Piwkowska, Pospischil, Brette, Sliwa, Rudolph-Lilith, Bal and Destexhe, 2008, Prescott and De Koninck, 2003, Shu, Hasenstaub, Badoual, Bal and Destexhe, 2005, Wolfart, Debay, Le Masson, Destexhe and Bal, 2005, Chance, Abbott and Reyes, 2002).

To this end, one needs first to generate an appropriate model of stochastic synaptic activity because thousands of synapses releasing randomly cannot be simulated in real time. The “point-conductance” stochastic process outlined above (Eqs. 9.1 to 9.3) constitutes a possible basis of such experiments (Fig. 9.6A). This stochastic process is adjusted to match the total conductance seen at the soma in the presence of synaptic noise in vivo. These conductances are then injected in dynamic-clamp (Fig. 9.6A) in order to reproduce, for instance, the conductance measurements in TTX experiments (Fig. 9.6B; compare with Fig. 9.2C). Other properties such as the mean and standard deviation of the \( V_m \), the spontaneous firing rate, the variability of spiking, or the power spectrum of the \( V_m \) fluctuations, can also be used to better constrain the model.

One of the properties of high-conductance states, namely the enhanced responsiveness, was thoroughly tested in dynamic-clamp experiments. Injection of stochastic conductances into cortical neurons in vitro profoundly altered their responsiveness, or equivalently, neuronal gain (Fellous, Rudolph, Destexhe and Sejnowski, 2003, Marsalek, Koch and Maunsell, 1997).
**Fig. 9.6.** Dynamic-clamp addition of synaptic noise in cortical and thalamic neurons *in vitro*.

A. Scheme of the dynamic-clamp experiment, in which computer-generated stochastic conductances are injected in the neuron *in vitro*. B. Injection of conductances in cortical neurons can re-create high-conductance states compatible with *in vivo* measurements (modified from (Destexhe, Rudolph, Fellous and Sejnowski, 2001)). C. Effect of controlling the amount of noise on the slope of the response curve of cortical neurons (modified from (Shu, Hasenstaub, Badoual, Bal and McCormick, 2003)). D. Effect of synaptic noise in thalamic neurons. The conductance noise interacts with burst generation to generate response curves that are roughly independent of the $V_m$ (modified from (Wolfart, Debay, Le Masson, Destexhe and Bal, 2005)).

Prescott and De Koninck, 2003, Shu, Hasenstaub, Badoual, Bal and McCormick, 2003, Chance, Abbott and Reyes, 2002). The “noise” component of background activity was found to reduce the gain in most cases, as illustrated in Fig. 9.6C. However, in some cases, noise may increase the gain (Fellous, Rudolph, Destexhe and Sejnowski, 2003), a property which could be explained by the presence of strong after-hyperpolarization conductances (Higgs, Slee and Spain, 2006).

The effect of synaptic noise was also studied in neuronal types which express
strong and prominent intrinsic properties, such as the bursting neurons of the thalamus. Thalamic relay cells classically display two modes of firing (Llinas and Jahnsen, 1982): at depolarized potentials, they respond to excitatory stimuli rather classically, by producing regular trains of spikes ("tonic mode"); at hyperpolarized potentials, the same stimuli evoke full-blown bursts of action potentials ("burst mode"). However, this classification has been challenged recently in a dynamic-clamp study where high-conductance states were reproduced in thalamic neurons (Wolfart, Debay, Le Masson, Destexhe and Bal, 2005). Instead of responding in two distinct modes, thalamic relay neurons with noise mixed single-spike and burst responses at all membrane potentials. This suggests that both single-spikes and bursts participate equally in transmitting information. Consistent with this, if one calculates spiking probabilities by mixing bursts and single-spikes, the responsiveness is independent of both the \( V_m \) level and the frequency of the input (Fig. 9.6D). In this case, this situation is possible only because of the presence of the calcium current generator of bursts. It was suggested that this constitutes an efficient "relay" for thalamic neurons (Wolfart, Debay, Le Masson, Destexhe and Bal, 2005), and this relay is possible only because of the interaction between intrinsic neuronal properties and synaptic noise.

In summary, dynamic-clamp experiments support the idea that stochastic conductances stemming from intense network activity are responsible for an enhancement of responsiveness in cortical neurons, and, more generally, a fundamental change of responsiveness in all neuronal types. Moreover, the amount of conductance and \( V_m \) fluctuations identified \textit{in vivo} are mostly in the range needed to drastically alter the responsiveness of neurons, which suggests that these phenomena occur well within the physiological situation. It is also one of the bases by which different "states" of activity of the network can yield different responsiveness (reviewed in (Destexhe and Contreras, 2006)). This is in agreement with previous observations that state changes induced by stimulating the ascending activating systems lead to enhanced responsiveness (Singer, Tretter and Cynader, 1976, Steriade, 1970).

9.5 Methods of analyzing experimental data

We have seen above that the point-conductance stochastic process (Eqs. 9.1 to 9.3) not only models the conductance fluctuations during background activity \textit{in vivo}, but can also be used to re-recreate \textit{in vivo}-like states in real neurons. In this section, we will go one step further and show that the same model can also be used as the basis for methods to analyze experimental data.

9.5.1 The VmD method to extract conductances from \( V_m \) activity

9.5.1.1 Outline of the VmD method The model described by Eqs. 9.1 to 9.3 has been thoroughly studied theoretically and numerically. Different analytic approximations have been proposed to describe the steady-state distribution of the \( V_m \) activity of the PC model (Lindner and Longtin, 2006, Richardson, 2004, Rudolph and Destexhe, 2003b, Rudolph and Destexhe, 2005) for a comparative
study, see (Rudolph and Destexhe, 2006). One of these expressions is invertible (Rudolph and Destexhe, 2003b, Rudolph and Destexhe, 2005), which enables one to directly estimate the synaptic conductance parameters \( (g_{e0}, g_{i0}, \sigma_e, \sigma_i) \) from experimentally obtained \( V_m \) distributions. This constitutes the basis of the VmD method (Rudolph, Piwkowska, Badoual, Bal and Destexhe, 2004), which we outline below.

The essential idea behind the VmD method is to fit an analytic expression to the steady-state subthreshold \( V_m \) distribution obtained experimentally, and obtain estimates of the parameters (mean, variance) of the underlying synaptic conductances. Among the different analytic expressions outlined above, we consider the following steady-state probability distribution \( \rho(V) \) for the membrane potential \( V \) (Rudolph and Destexhe, 2005, Rudolph and Destexhe, 2003b):

\[
\rho(V) = N \exp \left[ \frac{u_e(V - E_e)^2}{(aC_m)^2} + \frac{u_i(V - E_i)^2}{(aC_m)^2} \right] + A_2 \arctan \left[ \frac{u_e(V - E_e) + u_i(V - E_i)}{(E_e - E_i)\sqrt{u_e u_i}} \right],
\]

where the following constants were defined: \( k_L = 2aC_m g_L, k_e = 2aC_m g_{e0}, \)
\( k_i = 2aC_m g_{i0}, u_e = \sigma_e^2 \hat{\tau}_e, u_i = \sigma_i^2 \hat{\tau}_i, \) as well as the following voltage-independent terms:

\[
A_1 = \frac{-k_L + k_e + k_i + u_e + u_i}{2(u_e + u_i)}
\]

and

\[
A_2 = 2aC_m \frac{(g_{e0}u_i - g_{i0}u_e)(E_e - E_i) - agL u_e(E_e - E_L) - agL u_i(E_i - E_L) + I_{ext}(u_i + u_e)}{(E_e - E_i)\sqrt{u_e u_i(u_e + u_i)}}
\]

Here, \( N \) denotes a normalization constant such that \( \int_{-\infty}^{\infty} dV \rho(V) = 1 \). \( \hat{\tau}_{\{e,i\}} \) are effective time constants given by (Rudolph and Destexhe, 2005), see also (Richardson, 2004):

\[
\hat{\tau}_{\{e,i\}} = \frac{2\tau_{\{e,i\}} \hat{\tau}_m}{\tau_{\{e,i\}} + \hat{\tau}_m},
\]

where \( \hat{\tau}_m = C/(G_L + g_{e0} + g_{i0}) \) is the effective membrane time constant.

Due to the multiplicative coupling of the stochastic conductances to the membrane potential, the \( V_m \) probability distribution (Eq. 9.4) takes in general an asymmetric form. However, \( \rho(V) \) shows only small deviations from a Gaussian distribution, suggesting an approximation by a symmetric distribution. To this end, the first and second order terms in the power series expansion of the exponent in Eq. 9.4 around the maximum \( \bar{V} \) of the probability distribution \( \rho(V) \)

\[
\bar{V} = \frac{S_1}{S_0},
\]
with \( S_0 = k_L + k_c + k_i + u_c + u_i \) and \( S_1 = k_L E_L + k_c E_c + k_i E_i + u_c E_c + u_i E_i \) are considered. This yields the following Gaussian distribution

\[
\rho(V) = \frac{1}{\sqrt{2\pi\sigma_V^2}} \exp \left[-\frac{(V - \bar{V})^2}{2\sigma_V^2}\right] \tag{9.7}
\]

with the standard deviation given by

\[
\sigma_V^2 = \frac{S_0^3(u_c E_c^2 + u_i E_i^2) - 2S_0S_1(u_c E_c + u_i E_i) + S_1^2(u_c + u_i)}{S_0^3}. \tag{9.8}
\]

This expression provides an excellent approximation of the \( V_m \) distributions obtained from models and experiments (Rudolph, Piwkowska, Badoual, Bal and Destexhe, 2004), because the \( V_m \) distributions obtained experimentally show little asymmetry (for up-states and activated states; for specific examples, see (Piwkowska, Pospischil, Brette, Sliwa, Rudolph-Lilith, Bal, Rudolph and Destexhe, 2005, Rudolph, Piwkowska, Badoual, Bal and Destexhe, 2004, Rudolph, Pospischil, Timofeev and Destexhe, 2007)).

The main advantage of this Gaussian approximation is that it can be inverted, which leads to expressions for the synaptic noise parameters as a function of the \( V_m \) measurements, specifically \( \bar{V} \) and \( \sigma_V \). By fixing the values of \( \tau_e \) and \( \tau_i \), which are related to the decay time of synaptic currents and which can be estimated from voltage-clamp data and/or current-clamp by using power spectral analysis (see Section 9.5.2.2), we have four parameters remaining to estimate: the means \( (g_{e0}, g_{i0}) \) and standard deviations \( (\sigma_e, \sigma_i) \) of excitatory and inhibitory synaptic conductances. To extract these four conductance parameters from the membrane probability distribution, Eq. 9.7 is, however, insufficient because it is characterized by only two parameters \( (\bar{V}, \sigma_V) \). To solve this problem, one possibility is to consider two \( V_m \) distributions obtained at two different constant levels of injected current \( I_{ext1} \) and \( I_{ext2} \). In this case, the Gaussian approximation of the two distributions gives two mean \( V_m \) values, \( \bar{V}_1 \) and \( \bar{V}_2 \), and two standard deviation values, \( \sigma_{V1} \) and \( \sigma_{V2} \). The resulting system of four equations relating \( V_m \) parameters to conductance parameters can now be solved for four unknowns, yielding

\[
g_{(e,i)0} = \frac{(I_{ext1} - I_{ext2}) \left[ \sigma_{V2}^2 (E_{(i,e)} - \bar{V}_1)^2 - \sigma_{V1}^2 (E_{(i,e)} - \bar{V}_2)^2 \right] \{E_e - \bar{V}_1\}(E_i - \bar{V}_2) + (E_e - \bar{V}_2)(E_i - \bar{V}_1)\} \{E_{(e,i)} - E_{(i,e)}\} \{V_1 - V_2\} \tag{9.9}
\]

\[
= \frac{(I_{ext1} - I_{ext2})(E_{(i,e)} - \bar{V}_2) + [I_{ext2} - G_L(E_{(i,e)} - E_L)](V_1 - V_2)}{(E_{(e,i)} - E_{(i,e)}) (V_1 - V_2)}.
\]

\[
\sigma_{(e,i)}^2 = \frac{2C(I_{ext1} - I_{ext2}) \left[ \sigma_{V1}^2 (E_{(i,e)} - \bar{V}_2)^2 - \sigma_{V2}^2 (E_{(i,e)} - \bar{V}_1)^2 \right]}{\bar{\tau}_{(e,i)} \left\{ (E_e - \bar{V}_1)(E_i - \bar{V}_2) + (E_e - \bar{V}_2)(E_i - \bar{V}_1) \right\} \{E_{(e,i)} - E_{(i,e)}\} (V_1 - V_2)^2} \tag{9.10}
\]

These relationships enable us to estimate global characteristics of network activity such as mean excitatory \( (g_{e0}) \) and inhibitory \( (g_{i0}) \) synaptic conductances,
as well as their respective variances ($\sigma^2_e$, $\sigma^2_i$), from the knowledge of only the $V_m$ distributions obtained at two different levels of injected current. This VmD method was tested using computational models (Fig. 9.7A) and dynamic-clamp experiments (Fig. 9.7B-C; Rudolph, Piwkowska, Badoual, Bal and Destexhe, 2004; see below) and was also used to extract conductances from different experimental conditions in vivo (Rudolph, Pelletier, Pare and Destexhe, 2005, Rudolph, Pospischil, Timofeev and Destexhe, Zou, Rudolph, Roy, Sanchez-Vives, Contreras and Destexhe, 2005). This will be examined in more detail in the next sections.

9.5.1.2 Testing the VmD method with dynamic-clamp Taking advantage of the possibility given by the dynamic-clamp technique (see above) to mimic in a finely controlled way the fluctuating conductances $g_e$ and $g_i$ in biological neurons, we performed in vitro tests of the VmD method (Piwkowska, Pospischil, Brette, Sliwa, Rudolph-Lilith, Bal and Destexhe, Piwkowska, Rudolph, Badoual, Destexhe and Bal, 2005, Rudolph, Piwkowska, Badoual, Bal and Destexhe, 2004). In a first test (in 5 neurons), we computed $V_m$ distributions selectively during periods of subthreshold activity collected within up-states recorded in ferret cortical slices, we subsequently extracted conductance parameters from Gaussian fits to these distributions, and, finally, we used the estimated parameters to inject fluctuating conductances in dynamic-clamp in the same cell, during down-states. Fig. 9.7C shows a typical example of a real up-state and, shortly after, an up-state re-created in dynamic-clamp. We confirmed that the $V_m$ distributions are very similar in the two cases (see (Rudolph, Piwkowska, Badoual, Bal and Destexhe, 2004) for more details). This test shows that the $V_m$ distributions observed experimentally in vitro during recurrent cortical activity can be accounted for by the proposed point-conductance model. We also re-estimated known parameters of synaptic conductances ($g_{e0}$, $g_{i0}$, $\sigma_e$, $\sigma_i$) injected in dynamic-clamp from the resulting $V_m$ distributions: the match between actual and estimated values is shown in Fig. 9.7B. This second test indicates that the passive approximation for the membrane behavior holds in the case studied. In these tests, we did not consider the issue of the estimation of $\tau_e$ and $\tau_i$ and assumed these values were known.

9.5.1.3 Application of the VmD method to analyze intracellular recordings in vivo The VmD method was applied to analyze intracellular recordings in anesthetized (Rudolph, Pelletier, Pare and Destexhe, 2005), as well as naturally sleeping and awake cats (Rudolph, Pospischil, Timofeev and Destexhe, 2007). We illustrate the latter study here. The VmD method was applied to several cells recorded in either awake or sleep states (Fig. 9.8A), sometimes displaying both states in the same cell. The analysis was based on $V_m$ distributions computed at different DC levels corresponding to the linear portion of the I-V curve of the recorded neurons (Fig. 9.8B). For both awake and sleep states, in the majority of cells analyzed, especially during slow-wave-sleep up-states, the inhibitory conductances were larger than excitatory ones, for both mean and variance (Fig. 9.8C). At the population level, the ratio of inhibition to excitation was higher during slow-wave-sleep up-states compared to the awake state. In 3 neurons that
**Fig. 9.7.** Numerical and dynamic-clamp test of the VmD method to extract conductances.

A. Simulation of the point-conductance model (top trace) and comparison between numerically computed \( V_m \) distributions (bottom; left) and the analytic expression (black; conductance values shown in the bar graph). B. Dynamic-clamp injection of the point-conductance model in a real neuron. (Right) Conductance parameters are re-estimated (black bars; error bars are standard deviations obtained when the same injected conductance parameters are re-estimated in different cells) from the \( V_m \) distributions and compared to the known parameters of the injected conductances (grey bars). (Left) The experimental \( V_m \) distributions are compared to the analytic distributions calculated using the re-estimated conductance parameters. C. Comparison of a spontaneous up-state (Natural up-state) with an artificial up-state recreated using conductance injection (Dynamic-clamp). Modified from (Rudolph, Piwkowska, Badoual, Bal and Destexhe, 2004).
were recorded from across several states, both average conductances together with their variances decreased in the awake state compared to slow-wave-sleep up-states. In addition, especially during the awake state, some cells displayed comparable excitation and inhibition or even a dominant excitation (2 out of 11 cells in the awake state). There was an important diversity in the absolute values of the estimated conductance parameters (Fig. 9.8D).

9.5.2 Other methods derived from the point-conductance stochastic model

9.5.2.1 Extraction of spike-triggered average conductances from $V_m$ activity We recently developed a procedure to extract the spike-triggered averages (STAs) of conductances from recordings of the $V_m$ (Pospischil, Piwkowska, Rudolph, Bal and Destexhe, 2007). The basis of the STA method is to, first, calculate the STA of the $V_m$ activity, and then search for the “most likely” spike-related conductance time courses $(g_e(t), g_i(t))$ that are compatible with the observed voltage STA. This problem is non-trivial because the membrane equation must be inverted, which is in general not possible because of the multiplicative coupling of conductances. However, assuming that the conductances are Gaussian stochastic processes (as in the point-conductance model), and by discretizing the time axis, it is possible to estimate the most probable conductance time course (“maximum likelihood” approach). To do this, one discretizes time, leading to sequences $\{g^k_e, g^k_i\}_{k=1,...,n}$, denoting the time course of conductances giving rise to the voltage STA $V^k$. For a given time $k$, there is a continuum of combinations $\{g^j_e, g^j_i\}_{j=0,...,n}$ to occur that reproduce a given voltage trace $\{V^l\}_{l=1,...,n+1}$:

$$p = \prod_{k=0}^{n-1} p^k,$$

(9.11)

where it can be shown (Pospischil, Piwkowska, Rudolph, Bal and Destexhe, 2007) that

$$p_k = \frac{1}{2\pi} \exp \left( -\frac{1}{4\Delta t} X^k \right)$$

(9.12)

with

$$X^k = \frac{\tau_e}{\sigma^2_e} \left( g^k_{e} - g^k_{e}(1 - \frac{\Delta t}{\tau_e}) - \frac{\Delta t}{\tau_e} g^0_{e} \right)^2 + \frac{\tau_i}{\sigma^2_i} \left( g^k_{i} - g^k_{i}(1 - \frac{\Delta t}{\tau_i}) - \frac{\Delta t}{\tau_i} g^0_{i} \right)^2,$$

(9.13)

where $\Delta t$ is a fixed time bin. This system can be solved by finding the extremum of $p_k$:

$$\left\{ \frac{\partial p}{\partial g^k_e} = 0 \right\}_{k=1,...,n}.$$
Fig. 9.8. VmD estimates of conductances from intracellular recordings in awake and naturally sleeping cats.

A. Intracellular recordings in awake and naturally sleeping (SWS) cats. Recordings were made in association cortex (area 5-7). B. Examples of Vm distributions computed during wakefulness (Awake) and slow-wave sleep up-states (SWS). The black lines show analytic fits of the experimental distributions. Insets: current-voltage relations obtained for these particular neurons. C. Conductance values estimated using the VmD method. Results for the means ($g_{e0}$, $g_{i0}$) and standard deviations ($\sigma_e$, $\sigma_i$) of excitatory and inhibitory conductances, respectively, as well as their ratios are shown (error bars: standard deviations obtained by repeating the analysis using different pairs of injected current levels). D. Grouped data showing the means and standard deviations of the conductances for different cells across different behavioral states (REM = Rapid Eye Movement sleep). Modified from (Rudolph, Pospischil, Timofeev and Destexhe, 2007).
leading to a simple linear system solvable by traditional methods (see details in (Pospischil, Piwkowska, Rudolph, Bal and Destexhe, 2007)).

Thus, as can be seen from Eq. 9.13, the STA of the conductances can be evaluated from a voltage trace at a single current level, but it requires prior knowledge of the parameters $g_{e0}$, $g_{i0}$, $\sigma_e$ and $\sigma_i$, which can be estimated using the VmD method (see above).

Similarly to the VmD method, the STA method was tested in two ways: First, using computational models, we verified that the procedure applied to the $V_m$ activity reproduces the STA of the conductances calculated from the model (Pospischil, Piwkowska, Rudolph, Bal and Destexhe, 2007). Second, we used the dynamic-clamp technique to inject known conductance patterns in real neurons. From the analysis of the $V_m$ activity, one could check that the STA method successfully estimates the correct conductance patterns related to spikes (Pospischil, Piwkowska, Rudolph, Bal and Destexhe, 2007).

The STA method was applied to intracellular recordings in awake and naturally sleeping cats (Rudolph, Pospischil, Timofeev and Destexhe, 2007). We found that for the majority of neurons, the spike is correlated with a decrease of inhibitory conductance, suggesting that inhibition is most effective in determining spiking activity. This observation matches the dominance of inhibition observed using the VmD method in the same neurons (see above).

### 9.5.2.2 Extraction of synaptic time constants from the power spectrum of the $V_m$

Another important way of analyzing $V_m$ recordings is through the power spectral density (PSD). The PSD of the $V_m$ fluctuations of the point-conductance stochastic process can be well approximated by the following expression (Destexhe and Rudolph, 2004):\[
S_V(\omega) = \frac{4}{G_T^2} \frac{1}{1 + \omega^2 \tau_m^2} \left[ \frac{\sigma_e^2 \tau_e (E_e - \bar{V})^2}{1 + \omega^2 \tau_e^2} + \frac{\sigma_i^2 \tau_i (E_i - \bar{V})^2}{1 + \omega^2 \tau_i^2} \right], \tag{9.14}
\]
where $\omega = 2\pi f$, $f$ is the frequency, $G_T = G_L + g_{e0} + g_{i0}$ is the total membrane conductance, $\tau_m = C/G_T$ is the effective time constant, and $\bar{V} = (G_L E_L + g_{e0} E_e + g_{i0} E_i)/G_T$ is the average membrane potential. The “effective leak” approximation used to derive this equation consisted of incorporating the average synaptic conductances into the total leak conductance, and then assuming that fluctuations around the obtained mean voltage are subjected to a constant driving force (Destexhe and Rudolph, 2004).

Fitting this template to experimentally-recorded PSDs should provide estimates of the synaptic time constants $\tau_e$ and $\tau_i$. This procedure was first tested by comparing the prediction to numerical simulations of a single-compartment model subject to fluctuating synaptic conductances (Eqs. 9.1 to 9.3). The matching between the analytic expression and the PSD obtained numerically was nearly perfect (Destexhe and Rudolph, 2004). The same procedure was also tested in dynamic-clamp (Piwkowska, Pospischil, Brette, Sliwa, Rudolph-Lilith, Bal and Destexhe, 2008).

In this case, the theoretical template provided an excellent fit up to frequencies of about 500 Hz, above which the mismatch was presumably due to instrumental noise.
This procedure was also used to fit in vivo recordings of $V_m$ activity (Rudolph, Pelletier, Pare and Destexhe, 2005). In this case, the matching was more approximate: the PSD presents a frequency scaling region at high frequencies ($>100$ Hz) which scales as $1/f^\alpha$ with an exponent $\alpha = 4$ predicted by the theory. The experimental PSDs show a different scaling at high frequencies, with an exponent close to $\alpha = 2.5$ (Destexhe, Rudolph, Paré et al., 2003, Rudolph, Pelletier, Pare and Destexhe, 2005). This different scaling may be due to the attenuation of synaptic inputs occurring on dendrites, as well as to the non-ideal aspect of the membrane capacitance (Bedard and Destexhe, 2008). Nevertheless, the matching of the expression above to the low-frequency end ($<100$ Hz) of the PSD yielded values of time constants of $\tau_e = 3$ ms and $\tau_i = 10$ ms. Small variations (around 20-30%) around these values of $\tau_e$ and $\tau_i$ yielded equally good fits (Rudolph, Pelletier, Pare and Destexhe, 2005). Thus, we conclude that this PSD method cannot be used to precisely estimate those parameters, but can nevertheless be used to broadly estimate them with an error of the order of 30%.

9.6 Conclusions

In this chapter, we have given an overview of the use of stochastic processes in the study of synaptic noise in cortical neurons. We first reviewed experimental results (Section 9.2), showing that cortical neurons in vivo are subject to a considerable amount of synaptic noise. In Section 9.3, we reviewed models of synaptic noise, and in particular the point-conductance stochastic process. This and other models have predicted a number of computational consequences of synaptic noise on neuronal processing. The rest of the chapter was devoted to illustrating the usefulness of the point-conductance stochastic process: it can be used to add artificial synaptic noise in neurons in vitro using the dynamic-clamp technique (Section 9.4). This technique is of primary importance, because it allows one to directly test the predictions of the models in real neurons. It can also be used to realize experiments that would not be possible in vivo, such as controlling the amount of synaptic noise. Another important application of the point-conductance model is that it can form the basis of the design of methods to analyze experimental data (Section 9.5). These methods include the estimation of synaptic conductances (the VmD method), spike-triggered average conductances (the STA method) or synaptic time constants (the PSD method). These quantities are evaluated from the knowledge of only the $V_m$ activity, which makes it applicable to the standard intracellular recording conditions. Each of these methods was tested using computational models, as well as on real neurons using the dynamic-clamp technique.

Thus, the drastic effect of noise on neurons, which was predicted by theoretical and computational studies, is now at the stage of being investigated in real neurons in two ways. First, the nature of synaptic noise is being characterized from experimental data using appropriate methods, which characterize different quantities such as the $V_m$ distributions and PSD, and derive the characteristics of the underlying synaptic conductances. Second, predictions of the models are being tested in real neurons, as we examine in more detail below.
The first prediction, namely that the gain and responsiveness of neurons is enhanced by noise, was first reported from modeling studies (Hö and Destexhe, 2000), and then investigated experimentally using dynamic-clamp injection of in vivo-like synaptic noise (Destexhe, Rudolph, Fellous and Sejnowski, 2001, Fellous, Rudolph, Destexhe and Sejnowski, 2002, Higgs, Slee and Spain, 2006, Piwkowska, Pospischil, Brette, Sliwa, Rudolph-Lilith, Bal and Destexhe, 2008, Prescott and De Koninck, 2003, Shu, Hasenstaub, Badoual, Bal and McCormick, 2003, Wolfart, Debay, Le Masson, Destexhe and Bal, 2005, Chance, Abbott and Reyes, 2002), confirming some of the predictions formulated by models. Enhanced responsiveness was also tested using real network activity, but contradictory results were obtained when comparing responses in up- and down-states (see Section 9.2). A possible reason for the discrepancies is that some of these studies used a unique input amplitude which is insufficient (inputs can be either more or less responsive depending on their amplitude; see Fig. 9.3B). More experiments are needed, using a range of different input amplitudes. A fascinating possible consequence is that the enhanced responsiveness due to synaptic noise could be used as an attentional mechanism (Hö and Destexhe, 2000, Shu, Hasenstaub, Badoual, Bal and McCormick, 2003). By modulating the amount of synaptic noise, it should be possible to switch entire networks from unresponsive to responsive states. This possibility should be investigated by designing appropriate experiments and models.

A second aspect concerns the modulation of intrinsic neuronal properties. Synaptic noise affects neuronal responsiveness, but what happens when neurons express dominant intrinsic properties, such as bursting? This question was addressed so far only for thalamic neurons (Wolfart, Debay, Le Masson, Destexhe and Bal, 2005). This study revealed that the classic “tonic” and “burst” modes of firing in thalamic relay cells were profoundly altered. With synaptic noise, these modes are no longer distinguishable because bursts and single-spikes participate to all responses. It was also shown that strong potassium conductances can change the sign of gain modulation in cortical neurons (Higgs, Slee and Spain, 2006). How extrinsic noise interacts with intrinsic neuronal properties is at present only partially understood, and certainly constitutes a field where much remains to be done.

A third prediction is that synaptic noise modulates dendritic integration. The phenomenon of enhanced responsiveness also influences local dendritic processing. The interplay between excitable properties (dendritic spikes) and synaptic noise can result in an equalization of the efficacy of individual synapses (Fig. 9.4). These predictions have so far not been tested experimentally; it would require one to recreate the correct conductance state all along the cable structure, which is at present difficult to achieve. More generally, how synaptic noise influences dendritic integration is a complex problem only partially understood, and which will also require further modeling and experimental studies.

A fourth prediction is that synaptic noise enhances the temporal resolution of neurons. This type of temporal processing was the first consequence put forward by modeling studies (Barrett, 1975, Bernander, Douglas, Martin and Koch, 1991, Holmes and Woody, 1989, Rudolph and Destexhe, 2003a, Rudolph and Destexhe, 2003c).
Neurons in high-conductance states necessarily have a smaller time constant which allows sharp temporal processing (see example in Fig. 9.5). Surprisingly, few experimental studies have investigated this aspect, which also constitutes a very interesting direction to be explored in the future.

As a conclusion, the exploration of synaptic noise and its effect on neurons and networks is a fascinating subject, which can have far-reaching consequences. The understanding of how the state of a network in general modulates the integrative properties and information flow (and vice-versa) is only at its early stage, and will require a continuous association of experiments and computational models.

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9.7 Bibliography


Synaptic “noise”


