Stochastic Resonance Improves Signal Detection in Hippocampal CA1 Neurons

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Stacey, William C. and Dominique M. Durand. Stochastic resonance improves signal detection in hippocampal CA1 neurons. J. Neurophysiol. 83: 1394–1402, 2000. Stochastic resonance (SR) is a phenomenon observed in nonlinear systems whereby the introduction of noise enhances the detection of a subthreshold signal for a certain range of noise intensity. The nonlinear threshold detection mechanism that neurons employ and the noisy environment in which they reside makes it likely that SR plays a role in neural signal detection. Although the role of SR in sensory neural systems has been studied extensively, its role in central neurons is unknown. In many central neurons, such as the hippocampal CA1 cell, very large dendritic trees are responsible for detecting neural input in a noisy environment. Attenuation due to the electrotonic length of these trees is significant, suggesting that a method other than passive summation is necessary if signals at the distal ends of the tree are to be detected. The hypothesis that SR plays an important role in the detection of distal synaptic inputs first was tested in a computer simulation of a CA1 cell and then verified with in vitro rat hippocampal slices. The results clearly showed that SR can enhance signal detection in CA1 hippocampal cells. Moreover, high levels of noise were found to equalize detection of synaptic signals received at varying positions on the dendritic tree. The amount of noise needed to evoke the effect is compared with physiological noise in slices and in vivo.

INTRODUCTION

Stochastic resonance (SR) is a phenomenon whereby the detection of a low-level signal is enhanced in a nonlinear system by the introduction of noise. SR originally was used to explain the periodicity of ice ages (Benzi et al. 1981) and since also has been detected in Schmitt triggers (Fauve and Heslot 1983), ring lasers (McNamara et al. 1988), sensory neurons (Bulsara et al. 1991; Collins et al. 1996; Douglass et al. 1993; Levin and Miller 1996; Pei et al. 1996), and other applications (Wiesenfeld and Moss 1995). In each system, the detection of a subthreshold signal was improved when a certain level of noise was added. The discovery of SR in sensory neurons has led to new insights about the role of noise and signal detection in the peripheral nervous system.

The physiological effect of SR in neurons is enhancement of signal detection, which is a primary function in many neurons. SR is characterized by a specific relationship between the signal-to-noise ratio (SNR) and the noise intensity. This relationship, describing how random fluctuations will affect the crossing of a barrier, originally was derived based on Kramers rate theory and applied to bistable phenomena (for review, see e.g., Dykman et al. 1995; Moss et al. 1994; Wiesenfeld and Moss 1995). The theory then was expanded to include monostable (“circular”) states (Stocks et al. 1993; Wiesenfeld et al. 1994). Equation 1 is the monostable solution for SNR with varying amounts of noise, where $\varepsilon$ is the signal strength, $\Delta U$ is the threshold barrier height, and $D$ is the noise intensity.

\[
\text{SNR} \propto \left( \frac{\varepsilon \Delta U}{D} \right)^2 e^{-\frac{\Delta U}{2D}}
\]

The curve defined by Eq. 1 contains a resonant peak corresponding to the level of noise intensity that produces maximum SNR. This equation is valid for a periodic input into a monostable system, which is a good representation of a neuron receiving a periodic signal. Many sensory cells function in an inherently noisy background, which seemingly would make detection more difficult. For example, the crayfish mechanoreceptor is exposed to a persistent noisy input from turbulence in a stream. The noise created by the stream can improve signal detection due to the effects of SR (Douglass et al. 1993). Like sensory neurons, the primary function of many central neurons is signal detection in a noisy environment. SR has been observed in rat hippocampal brain slices when a sinusoidal signal and Gaussian noise are administered with parallel field electrodes to a slice in high-potassium solution (Gluckman et al. 1996). However, SR also could be involved in the detection of subthreshold synaptic inputs by central neurons with physiological noise sources.

In the CNS, determining what is “signal” and what is “noise” is a complex task. In terms of detection of any particular signal, any other input that is uncorrelated with that signal can be considered “noise” in SR analysis. This fact makes SR a powerful tool for analysis of signal detection in the CNS, especially when considering the number of connections some neurons have. Hippocampal CA1 cells have large apical dendritic trees that receive tens of thousands of synaptic inputs: a large potential noise source. Because multiple coactive synaptic connections are required to discharge the cell (Andersen 1990), there is a large potential source of subthreshold signals. In addition, the length of the apical dendrites ($\approx 500 \mu m$) produces a long electrotonic distance (Rall 1977). Synaptic inputs located at distal positions on the tree can attenuate to a point where they cannot have any significant summative effects on the soma (Spruston et al. 1993). Previous work has proposed that active channels in the dendrites could be responsible for amplifying the distal signals (Cook and Johnston 1997; Magee and Johnston 1995; Poolos and Kocsis 1990). SR...
describes an alternative mechanism capable of enhancing detection of distal synaptic inputs with the presence of noise. We have tested the hypothesis that SR can improve detection of subthreshold synaptic inputs in the presence of synaptic noise. Results were obtained using computer simulations of hippocampal CA1 cells and in vitro hippocampal slices. The noise levels capable of evoking SR were compared with published physiological noise data to evaluate the role of SR under normal physiological conditions.

METHODS

NEURON model

A CA1 cell was modeled with the neural modeling software NEURON (Hines 1993) with the parameters shown in Table 1. The neuron was constructed as shown in Fig. 1A using equivalent dendritic trees (Rall 1977). In the dendrites, the membrane specific resistance ($R_m$) was halved and capacitance ($C_m$) doubled to account for the increased surface area of dendritic spines (Spruston and Johnston 1992). The dendrites contained no active channels. The soma contained one sodium, one calcium, and four active potassium channels adapted from a previous model of CA1 cells (Warman et al. 1994) (see APPENDIX).

Synaptic transmission was simulated using a model of AMPA synapses. Equations 2 and 3 describe the current from the AMPA synapse, where $g_{\text{max}}$ is the peak conductance and $[O]$ is the fraction of open channels (Destexhe 1998; Destexhe et al. 1994, 1998).

\[
I_{\text{AMPA}} = g_{\text{max}} [O] (V - E_{\text{AMPA}}) \quad \text{(2)}
\]

\[
\frac{d[O]}{dt} = \alpha [T] (1 - [O]) - \beta [O] \quad \text{(3)}
\]

![FIG. 1.](image)

The NEURON model incorporated the specifications shown. Tau was set by choice of $R_m$ and $C_m$. $R_m$ was tested by current injection. * From Spruston and Johnston (1992).

The peak current amplitudes of both the synaptic input signal and the synaptic noise were adjusted by changing the $g_{\text{max}}$ parameter. For the remainder of this paper, $g_{\text{max}}$ will be used as the indicator of input amplitude. Each synaptic channel was designed to represent a population of synapses on a segment of the dendritic tree. The subthreshold signals to be detected were introduced as synaptic events occurring at 5 Hz with $g_{\text{max}}$ adjusted to a value that did not produce a somatic action potential. The noise signal was added to simulate random
synaptic events on the CA1 dendrites. Although spontaneous synaptic events contain both AMPA and N-methyl-D-aspartate (NMDA) receptor components (McBain and Dingledine 1992), only AMPA receptor components were used in this simulation because the AMPA portion dominates in normal artificial cerebrospinal fluid (ACSF) (Manabe et al. 1992). Each noise synapse fired action potentials independently at random intervals, a Poisson process (Cox and Lewis 1996). Events were triggered at random intervals by generating a uniform-distributed random number (0–1) at every time step and comparing it with a threshold value. Triggering occurred whenever the random number was lower than the threshold. For a uniform-distributed set of random numbers from 0 to 1, the cumulative distribution function yields $F_X(x) = x$, so the threshold parameter value was equal to the event probability for one time step. The threshold was chosen to produce noise events with a mean interval of 0.05 (20 Hz) and 0.01 s (100 Hz). A histogram and a power spectrum were obtained to verify the uniformity of the random-number generator and white spectrum of the random event frequency (data not shown). The amplitude of each noise event was modulated with the $g_{\text{max}}$ parameter. To plot the data as a function of noise intensity $D$, the variance of the input noise for each level of $g_{\text{max}}$ was computed by measuring the current entering the synapse. The variance was directly proportional to the square of the input amplitude.

**Experimental methods**

**PREPARATION OF SLICES.** Mature Sprague-Dawley rats were anesthetized and decapitated, and their brains were removed quickly. Surgery followed protocol approved by the University Animal Resource Center. Hippocampal slices 400-µm thick were cut using a Starrett tissue chopper and placed in a perfusion chamber. Slices were bathed for over an hour in room temperature ACSF consisting of (in mM) 124 NaCl, 3.75 KCl, 1.25 KH₂PO₄, 2 CaCl₂, 2 MgSO₄, 26 NaHCO₃, and 10 dextrose and aerated with 95% O₂-5% CO₂. Each slice was then transferred to another perfusion chamber and incubated to 35°C for implementation.

**ELECTRODE PLACEMENT AND SIGNAL GENERATION.** Tungsten microelectrodes were used to introduce signal and noise in the form of synaptic events on CA1 cells (see Fig. 2). The signal electrode was placed in the Schaffer collateral layer of the hippocampal slice. The noise electrode was placed in the stratum oriens. A glass microelectrode filled with 150 mM NaCl was used for extracellular recording in the CA1 region. Extracellular recording was amplified using an Axoclamp 2A and recorded onto digital audio tapes.

The “signal” consisted of a periodic train of 250-µs current pulses applied at 5 Hz. By injecting the signal pulses into the Schaffer collaterals, the signal reached CA1 cells as synaptic events on the apical dendrites. The amplitude of the signal was adjusted to produce a subthreshold extracellular response in CA1. The experimental threshold was chosen to be a 300-µV population spike, which was 10% of the peak CA1 response. This choice of threshold allowed evaluation of the average response of several neighboring CA1 cells.

This average measure was assumed to be an estimate of the response of a single cell and thus be comparable to the computer simulation. The “noise” was generated using a random signal as the trigger for 250-µs current pulses, producing uniform-amplitude current pulses at random intervals. The output of a random signal generator was used to trigger a voltage stimulator (Grass S88) that produced 250-µs, 5.1-V pulses when triggered. The voltage pulses then were converted to current pulses in a digital current isolation amplifier (A-M systems). The current pulses were injected into the stratum oriens to evoke synaptic events in the basal dendrites of CA1. The events were compared with those evoked by the “signal” electrode to ensure orthodromic, excitatory connections. This was done by comparing the evoked responses in each case to ensure the “noise” electrode produced field potentials of similar amplitude, duration, shape, and delay from stimulus artifact as the orthodromic stimulation in the Schaffer collaterals. Experiments were not performed unless the noise electrode had proper orthodromic connection. Pulse amplitude was adjusted manually with the output level controls on the digital amplifier. The mean frequency of noise events was controlled by adjusting the amplitude of the random signal. The experiment was performed using three different mean noise frequencies: 64, 97, and 145 Hz, which were chosen to be similar to the frequencies used in the simulations. For each frequency, the noise input was tested to insure a white spectrum above 2 Hz (data not shown).

Recorded voltage data were digitized at 4,000 Hz. The data were then filtered to eliminate the stimulus artifacts by masking any response in the immediate vicinity of a very large (>300 µV) spike (see Fig. 5A). The filtered data were converted to a detected output time series by evaluating when the extracellular voltage surpassed the 300-µV threshold. The output series therefore evaluated potentials between 300 µV and 3 mV. Care was taken to ensure that long baseline fluctuations (which caused potential changes for >10 ms) were not passed by the threshold. Visual inspection of the initial and final 2 s of data were performed on each recording to make this analysis. Because there was no direct measurement of the input variance on the CA1 cells, the SNR data were plotted as a function of the input amplitude squared, which should be proportional to the variance if one assumes a strong correlation between the stimulus amplitude and the resultant synaptic strength. Simulations were performed to verify this, as well as careful inspection of the curve fitting that resulted from using this substitution.

**EVALUATION OF SR.** In accordance with previous work on SR (Douglass et al. 1993; Gluckman et al. 1996; Wiesenfeld and Moss 1995), raw voltage data were converted to an output time series that contained binary pulses corresponding to the occurrence of action potentials (see Fig. 1B). The power spectral density (PSD) of the detected output was obtained in Matlab (50,000 point Hanning window; 45,000 point overlap). The SNR was calculated by dividing the power at 5 Hz by the average of the baseband noise power on both sides of the 5-Hz peak (see Fig. 1C). Therefore any action potential in phase with the input signal was regarded as “signal” by contributing power to the input signal frequency. Spikes that are not in phase with the...
the 5-Hz signal contribute to other frequencies, creating the baseband noise. Data were fitted to Eq. 1 by using the Microsoft Excel (Excel 97) solver to minimize the error by changing the \( \Delta U \) and \( e \) parameters.

RESULTS

Computer simulation

The goal of the simulations was to test whether detection of a subthreshold signal can be improved by SR with synaptic noise sources. The simulations investigated the noise characteristics necessary to produce SR in a CA1 cell model. The effect of both distributed and single noise sources on the SNR were tested.

DISTRIBUTED NOISE SOURCES. The model first was configured to generate noise at multiple synapses throughout the neuron simultaneously. An independent noise source was placed at each of the ten positions indicated by the crosses in Fig. 1A. This distribution is representative of the physiological synaptic noise in CA1 (Andersen 1990; Bekkers et al. 1990). Signal synapses were placed at three positions along the apical dendrite to model synaptic events located at different distances from the soma. The same input intensity \((g_{\text{max}})\) was used for each position. The intensity was chosen to be subthreshold for the distal positions (b and c) but above threshold at the proximal position (a). An independent simulation was performed for each signal position.

For the subthreshold positions b and c, increasing noise intensity caused a sharp increase in SNR up to a peak value followed by a tapered decrease in a manner characteristic of SR (Fig. 3A). Of note is that noise input corresponding to the physiological baseline had a significant effect (Fig. 3B, see DISCUSSION). Similar results were obtained for 100-Hz noise (not shown). As noted previously for neural systems, the re-

![Graph showing SNR vs. noise variance for 20 Hz and 100 Hz noise](image)

**Fig. 3.** SR in computational model with basal noise source. **A:** SNR obtained with 10 distributed noise sources. Response to signal at each of the 3 positions is shown with error bars for standard deviation. Data from positions b and c are shown fitted to the SR equation. At position a, SR is not present because the signal was not subthreshold. As the noise increases, SNR at position a decreases as expected. Detection at the subthreshold positions increases as predicted by SR. **B:** expanded plot from A, showing the SR effects even at very low noise levels. \(-\)-, input noise that resulted in 12,000 \( \mu \text{V}^2 \) variance at the soma, the physiological baseline. There are 1 data point in b and 2 in c that resulted in 0 SNR. **C:** equalizing effect of noise on detection of electrotonically distant signals for both 20- and 100-Hz noise. Data are arranged to show how detection for 4 different noise levels (shown in the legend in \( \mu \text{V}^2 \)) changes with electrotonic distance. Same data are in the “20 Hz noise” plot as in A. For small noise intensity (0.36 and 0.2 \( \mu \text{V}^2 \)), signal at positions b and c cannot be detected, whereas a has nearly perfect detection. As the noise increases, SNR at position a decreases. Detection at the subthreshold positions, however, increases as dictated by SR. For higher levels of noise, the difference in SNR between neighboring positions becomes progressively less. Of note are the nearly flat lines at higher noise levels, which was more pronounced for the 100-Hz noise. Although the SNR has been reduced greatly proximally, detection is much less dependent on the position of the inputs, equalizing signal detection from electrotonically distant inputs.
fractory period causes the output to overshoot Eq. 1 at higher noise variance (Wiesenfeld and Moss 1995). The more proximal synapse, b, reached a higher peak SNR at a lower value of noise than at position c. The difference corresponds to a change in the SR parameters in Eq. 1, in particular a smaller $\Delta U$ value. The effect of noise on detection of the suprathreshold signal (a) is quite different: noise progressively corrupts the SNR for the entire range of increasing noise intensity. The combination of the drop at position a and the SR characteristics of b and c creates a novel effect in neuronal signal detection. For higher levels of noise, the difference in SNR between neighboring positions becomes progressively smaller.

This equalizing effect is shown in Fig. 3C, where the SNR is plotted as a function of electrotonic distance for four noise levels. Although the SNR has been reduced greatly proximally, detection is much less dependent on the position of the inputs. Positions a and c are 400 $\mu$m apart, corresponding to an electrotonic length of 0.64. With low levels of noise, the difference in SNR at each position is large and signals at the proximal sources can be detected much better. As the noise intensity is increased, this difference is reduced and the SNR is more uniform along the length of the dendrite, corresponding to a nearly flat slope in Fig. 3C. The net result is that SNR is nearly independent of the position of the signal when high levels of noise are present (the SNR for 324-$\mu\text{A}^2$ noise variance is between 10 and 50 for all positions; at 23 $\mu\text{A}^2$, it ranges from 10 to 1980). The equalization was even more pronounced when the mean noise frequency was 100 Hz. With 100-Hz noise, 20-$\text{pA}^2$ noise intensity produces an SNR for the subthreshold position (b) that is nearly as high as the suprathreshold input position (a), which at an SNR of 1,000 can detect nearly every periodic signal pulse. Clearly, noise greatly improved the detection of the distal inputs, allowing them to be detected almost as well as the proximal inputs. Therefore these results suggest that SR due to synaptic noise not only improves detection of subthreshold signals in CA1 cells but also may preferentially aid detection of distal synapses during periods of high noise by decreasing dependence on input position.

SINGLE NOISE SOURCE. The model then was configured to analyze the effect of the number and position of the noise synapses on SR. A periodic synaptic signal was applied to position b on the apical dendrite. The minimum signal amplitude that produced a somatic action potential was $g_{\text{max}}^+ = 8$ nS; therefore the simulation was run using subthreshold values of 7 and 5 nS. A single noise synapse at the midpoint of the basal dendrite was activated (see Fig. 1A). Because only one source was active, the event probability was increased 10-fold from the distributed-source simulation to maintain mean noise frequencies of 20 and 100 Hz.

A single noise source produced the characteristic SR effect (Fig. 4A). For a signal of 7-nS amplitude, a synaptic noise input with variance $\leq 0.36$ pA$^2$ had no effect on signal detection; however, increasing noise variance to 3.2 pA$^2$ allowed detection of the signal with action potentials synchronized to the input signal. This input corresponded with the physiological level of noise recorded in slices (Fig. 4B, see DISCUSSION). As the noise signal was increased further to 900 pA$^2$, the noise itself generated action potential. The effect was much more pronounced for the 7-nS input, which was closest to threshold. Altering the strength of the signal had the same effect as changing input location in the previous simulation (changing $\Delta U$ and $e$ in Eq. 1). Similar results (not shown) were obtained for noise with a mean frequency of 100 Hz but had a slightly different SR curve: the peak values in the SNR plots were often nearly 10 times those obtained in corresponding simulations with 20-Hz noise and occurred at lower noise variance.

The noise source then was moved to four other positions (the soma and the midpoint of each of the apical branches) to determine the effect of position on signal detection. Each configuration was simulated separately. Similar results were obtained (not shown). The high similarity of the data from the five single noise positions suggests that location of the noise signal has much less effect on signal detection than noise variance and frequency. The presence of SR is determined by the input characteristics at the threshold-detecting element, the soma. Therefore we concluded that a single noise source can be used to approximate distributed physiological noise sources to produce SR and the effect was tested experimentally.

![FIG. 4. SNR obtained by single noise sources. A: signal synapse was placed at position b (Fig. 1A) and $g_{\text{max}}^+$ set to 2 subthreshold values. Data are fit to Eq. 1. Increased noise from 1 synapse produced SR just as in the previous simulation. Similar results were obtained when the single noise source was moved to different positions on the neuron. SNR improvement was greater for the signal closer to threshold. B: expanded plot from A, indicating physiological noise level. SNR for the 7-nS signal shows considerable improvement even at low noise.](http://jn.physiology.org/doi/10.1210/jn.0000000000000000)
Experimental results

To detect the presence of SR in CA1 cells, an in vitro experiment was designed to test the prediction of the second simulation protocol. Electrodes were placed in the stratum radiatum and s. oriens to introduce periodic inputs and random synaptic events, respectively (Fig. 2). Ten experiments were performed using slices from six different rats. Extracellular population spikes were recorded, and a threshold was chosen to represent a critical number of cells firing (a population spike of 200 mV). Noise improved detection of a subthreshold signal in all slices tested. An example of the effect of noise is shown in Fig. 5A. The addition of synaptic noise clearly improves detection of the signal within a certain range of noise intensity. All 10 experiments exhibited the characteristic SR curve (Fig. 5C). For low noise intensity, the SNR was increased, at times reaching values over 100, a result comparable with those obtained in the simulations. As the noise increased, it evoked action potentials independent of the periodic signal, adding false positive outputs and decreasing the SNR. There was no appreciable change in SR parameters for the three values of mean noise frequency generated (not shown). In addition to the subthreshold signal data, Fig. 5B shows the result of noise added to a suprathreshold signal. As demonstrated by the simulations (Fig. 3), high noise serves to equalize the detection of supra- and subthreshold signals. Although it is not possible to compare directly the noise levels used in the experiment and the simulation, the results are qualitatively the same. The SNR profiles for both the simulation and the experiment exhibited similar SR behavior. The SNR reached similar values and in both cases the data fit the SR equation.

FIG. 5. SR in hippocampal slices. A, top: reference input at 5 Hz. Bottom: raw extracellular voltage data. Noise pulses are added to the slice as shown by the bar above the data. Scale is indicated by the bar in the right. Large, thin spikes are truncated stimulation artifacts. - - -, threshold detected by the processing, ignoring artifacts. Output trace below the data shows the resultant detection, producing a time series detected output equivalent to those produced for the computer simulation in Fig. 1. Two boxed portions of the raw data and detected output are shown in expanded form as indicated. B: same slice as in A, except with a larger noise input. These data show how more noise causes “false” action potentials that decrease the SNR. C: averaged SNR data from 10 experiments are shown as a function of squared noise pulse amplitude. For all slices tested, amplitudes ≤400 nA² remained subthreshold. More than 3,600 nA², the slices began to saturate and the response degrade, so no values above this level were recorded. As seen in the data, the average response has the characteristic SR curve. Each of the 10 individual experiments showed similar results. Also included is the data from a typical supra-threshold signal. Comparison of the suprathreshold response with the average subthreshold response shows a result similar to that in Fig. 3C, where high noise variance equals the detection of supra- and subthreshold signals.
This is, to our knowledge, the first demonstration of SR in hippocampal neurons using synaptic inputs.

**DISCUSSION**

**SR can improve detection of distal signals**

SR in central neurons such as CA1 may help explain how distal synapses can be detected. Even with completely passive dendrites, we have shown that attenuated signals are detectable when synaptic noise is added to the neuron. SR thus explains a possible method that CA1 cells can use to improve detection of distal signals without the need for active channels in the dendrites.

Because the apical dendrites are so long, distal synapses in CA1 often are attenuated greatly and cannot generate action potentials. How do these distal synapses contribute to somatic integration? SR provides two answers to that question. First, because noise can improve detection, a source of noise is needed for there to be any effect. The high number of synapses in CA1 potentially provide a large, highly variable noise source. Second, our simulation has shown that SR can make detection less dependent on signal position. This finding agrees with experimental evidence showing that equivalent signals applied to various positions on the dendritic tree are detected equally at the soma (Andersen 1990), and is verified by the data in Fig. 5B, showing equalized detection of sub- and suprathreshold signals from a single position. Although this effect clearly relies on decreasing the fidelity of proximal signal detection, it provides a possible explanation of the experimental data using only passive dendrites. The effect could be enhanced if the model included active dendritic channels, which amplify distal signals (Magee et al. 1998). Because of these results, we suggest that SR using synaptic noise may serve to effectively decrease the electrotonic length in a cell, preferentially aiding detection of more distal synapses and decreasing dependence on input position under high-noise circumstances.

**Choice of synaptic inputs**

Although SR classically has been studied using sinusoidal input signals, the results reported here used a periodic pulse train input because pulses are required for synaptic inputs in most neurons. Our results agree with recent work showing that a pulse train can evoke SR (Chapeau-Blondeau et al. 1996). The periodicity of the input signal allows the use of power spectral density as a measure of the response to the signal input; however, an aperiodic input analyzed with other correlational methods would be expected to give similar SR results (Collins et al. 1996; Heneghan et al. 1996; Levin and Miller 1996; Pei et al. 1996). SR is therefore a method of improving detection of any signal in a neuron regardless of whether the signal is a sinusoid or even aperiodic.

**Physiological relevance of SR in CA1 neurons**

For the presence of SR in neurons to be relevant, the effect must occur within physiological noise levels. There are more than 10,000 synapses on each CA1 pyramidal cell (Andersen 1990), creating the potential for a significant amount of synaptic noise. Brain-slice experiments have shown an intracellular noise variance of \( \sim 12,000 \mu V^2 \) (Turner 1988; Wahl et al. 1997). To evaluate SR in CA1 cells, the noise levels used in the data need to be compared with this physiological level.

The somatic noise variance was calculated by recording the voltage at the soma for each level of noise intensity and computing the variance of each data set in square micromvolts. The synaptic input that produced 12,000 \( \mu V^2 \) at the soma was 1.7 \( \mu A^2 \). This baseline level is indicated by a dashed line in Figs. 3B and 4B. The baseline falls within a region where the SNR clearly is enhanced by the noise, especially for signals close to threshold. This result strongly suggests that endogenous noise can improve detection of subthreshold signals. Because even the noise present in a brain slice is capable of generating SR, it is probable that CA1 cells and many other CNS neurons use SR to detect small signals. Furthermore, because the baseline lies on the steep upward slope of the SR curve, any small increase in noise intensity will produce a large improvement in signal detection.

Although these results show that endogenous noise could play an important role in signal integration in CA1 cells, the peak SNR levels occur at noise intensities much higher than the baseline level. The peak for synapse b in Fig. 1C occurred at 181,900 \( \mu V^2 \). Can physiological noise produce such high variance, thereby maximizing the detection predicted by SR? The answer to this question requires consideration of several noise sources that exist in the neural tissue. Our model includes noise similar to spontaneous miniature excitatory postsynaptic potentials (mEPSPs) because they are random synaptic events on AMPA receptors. The frequency of mEPSPs has been shown to be only \( \sim 1 \text{ Hz} \) (Manabe et al. 1992; Wyllie et al. 1994), but to produce any noticeable effect, the frequency of the noise events had to be increased well 1 Hz. However, mEPSP frequency is quite dependent on experimental conditions such as stimulation frequency (Manabe et al. 1992), bath calcium (Raastad et al. 1992), and temperature (Finch et al. 1990) and is increased by paired pulse modulation (Mennerick and Zorumski 1995) and long-term potentiation (Malgaroli and Tsien 1992). In fact, noise representing only mEPSPs—1-Hz pulses injecting a charge of 100 fC (Bekkers and Stevens 1990; Goda and Stevens 1994; Larkman et al. 1997; Manabe et al. 1992)—produced a variance \( < 6,000 \mu V^2 \). This result agrees with the finding that minis produce only a fraction of the total endogenous noise in slices (Wahl et al. 1997). Other forms of random synaptic activity also will contribute to synaptic noise. For example, random axonal firing contributes to synaptic noise, evoking larger amplitudes than minis (Turner 1988; Wahl et al. 1997). Uncorrelated action potentials from CA3 cells can greatly increase noise variance because any signal uncorrelated with the desired input can be considered “noise” in terms of signal detection.

The most important sources of noise, however, are those not active in a slice preparation but present in vivo. In vivo recordings demonstrate that the normal input to the hippocampus is behavior dependent, containing theta rhythms (White et al. 1998), random pulse trains (Leung 1982), and the powerfully depolarizing sharp waves (Kamondi et al. 1998). Studies of other central neurons reveal that there exist active neuronal states in vivo that are not present in slices (Wilson and Kawaguchi 1996) and can increase baseline variance 100-fold (Destexhe and Paré 1999). Taking into account these additional sources, we estimate that even normal in vivo activity could...
easily produce background noise 100 times greater than the
12,000 \mu V^2 baseline observed in slices, placing the SNR of the
cell in the peak region of signal detection predicted by SR. This
agrees with previous work suggesting that arrays of neurons
have greatly increased detection (Moss and Pei 1995), an effect
that also has been studied in SR systems (Inchiosa and Bulsara
1995; Lindner et al. 1995). Therefore, the amplitude of the
noise can span a broad spectrum of variance, with a minimum
value 12,000 \mu V^2 and an arbitrarily large maximum level.
According to our simulations, this range encompasses the
entire region of interest of the SR equation for near-threshold
signals. Because of our finding that even minimum, endoge-
 nous noise levels are capable of producing SR, we hypothesize
that SR is present in any threshold-bearing central neuron for
signals near threshold. The neural response can be modulated
by factors affecting the background noise. Quiescent states,
with very low noise variance, will preferentially detect signals
close to threshold and be very sensitive to small changes in the
noise. Active states will move the SNR beyond the SR peak, to
the region where detection is less dependent on signal strength
or synaptic position. SR thus predicts a novel method of
modulating signal detection in the CNS.

Conclusion

Many systems have been shown to use SR as a method of
improving signal detection. Our results demonstrate that SR
can function in rat hippocampal CA1 cells using only synaptic
inputs for both signal and noise. The levels of noise necessary
for SR were within practical physiological limits. SR provides
a possible explanation for the finding that distal and proximal
synapses are detected equally. Other theories to explain this
phenomenon, such as the role of active voltage-gated channels
in the dendrites (Magee et al. 1998), could be synergistic with
SR to improve detection of the distal signals. SR can improve
detection of many different subthreshold signals and so may
help explain detection of low-amplitude inputs such as very
weak electric fields (Weaver and Astumian 1990) and ex-
 tremely low-frequency signals (Kavet and Banks 1986).
Perhaps most intriguing is the finding that even minimum noise
levels improve detection of some subthreshold signals. Noise
thus could play a major role in signal processing by CNS
neurons, both in slices and in vivo.

Appendix

CA1 neuron model

The model in Warman et al. (1994) was adapted for simulation of
the CA1 cell. A resting membrane potential of −66 mV was chosen
to equilibrate the membrane currents. Additional changes corrected
for the units used in NEURON and published errata. Except where
noted otherwise, all \alpha and \beta function for the channels were imple-
mented as published.

Sodium channel

\[ I_{Na} = g_{Na} m^4 h (V_m - E_{Na}) \]
\[ E_{Na} = 65 \text{ mV} \]

Calcium channel

\[ I_{Ca} = g_{Ca} r (V_m - E_{Ca}) \]
\[ E_{Ca} = -30.5 \log_{10} ([Ca_2]_o/2000) \]

Calcium concentration dynamics

\[ \frac{d([Ca_2]_o)}{dt} = -[([Ca_2]_o - 0.1)/\tau_f] + 3 \times 10^4 \delta(t)/wzFA \]
\[ \tau_f = 0.9 \text{ ms} \]
\[ [Ca_2, 2]_o \text{ was held constant at 0.13 } \mu M \]

The 10^4 factor corrects for units used in NEURON.

Potassium channels

\[ I_{CT} = g_{CT} c d(V_m - E_{K}) \]
\[ E_{K} = -80 \text{ mV} \]
\[ \alpha_c = -0.0077 (V_m + V_{shift} + 103) / [\exp((V_m + V_{shift} + 103)/12) - 1] \]
\[ \beta_c = 1.7 / \exp((V_m + V_{shift} + 237)/30) \]

The \( V_{shift}, \tau_{CT}, \) and \( d \) channel were used as published.

\[ I_{AHP} \]
\[ I_{AP} = g_{AP} q (V_m - E_{AP}) \]
\[ E_{AP} = 3.3 \text{ mS/cm}^2 \]

\[ I_A = g_{A} h (V_m - E_{A}) \]
\[ E_{A} = 6.7 \text{ mS/cm}^2 \]

\[ I_{AHP} = g_{A} h (V_m - E_{A}) \]
\[ E_{A} = 100 \text{ mS/cm}^2 \]

\[ I_{DR} = g_{DR} n (V_m - E_{DR}) \]
\[ E_{DR} = 6.7 \text{ mS/cm}^2 \]

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