Noise and Coupling Affect Signal Detection and Bursting in a Simulated Physiological Neural Network

WILLIAM C. STACEY1,2 AND DOMINIQUE M. DURAND1
1Department of Biomedical Engineering, Case Western Reserve University; and 2Department of Neurology, University Hospitals of Cleveland, Cleveland, Ohio 44106

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Signal detection in the CNS relies on a complex interaction between the numerous synaptic inputs to the detecting cells. Two effects, stochastic resonance (SR) and coherence resonance (CR), have been shown to affect signal detection in arrays of basic neuronal models. Here, an array of simulated hippocampal CA1 neurons was used to test the hypothesis that physiological noise and electrical coupling can interact to modulate signal detection in the CA1 region of the hippocampus. The array was tested using varying levels of coupling and noise with different input signals. Detection of a subthreshold signal in the network improved as the number of detecting cells increased and as coupling was increased as predicted by previous studies in SR; however, the response depended greatly on the noise characteristics present and varied from SR predictions at times. Careful evaluation of noise characteristics may be necessary to form conclusions about the role of SR in complex systems such as physiological neurons. The coupled array fired synchronous, periodic bursts when presented with noise alone. The synchrony of this firing changed as a function of noise and coupling as predicted by CR. The firing was very similar to certain models of epileptiform activity, leading to a discussion of CR as a possible simple model of epilepsy. A single neuron was unable to recruit its neighbors to a periodic signal unless the signal was very close to the synchronous bursting frequency. These findings, when viewed in comparison with physiological parameters in the hippocampus, suggest that both SR and CR can have significant effects on signal processing in vivo.

INTRODUCTION

The effect of noise on detection of subthreshold signals in threshold-detecting systems, or stochastic resonance (SR), has been investigated in several physiological and nonphysiological systems. SR theory was originally developed to describe a single bistable element (Benzi et al. 1981; Dykman et al. 1995; Moss et al. 1994) and was later expanded to describe a monostable system like a neuron (Stocks et al. 1993; Wiesenfeld et al. 1994). Both computer simulations and in vitro experiments have been used to demonstrate SR behavior in a number of neural systems (Braun et al. 1994; Bulsara et al. 1991; Collins et al. 1996; Douglass et al. 1993; Levin and Miller 1996; Pei et al. 1996; Russell et al. 1999). Recent studies in the CA1 layer of the hippocampus have indicated that SR can function to influence signal detection in this system (Gluckman et al. 1996, 1998; Stacey and Durand 2000) using endogenous noise sources (Stacey and Durand 2001). Even subtle changes above resting noise variance can improve the ability of neurons to detect subthreshold signals. The influence of noise on signal detection in CA1 is therefore quite significant and relevant to information processing in the brain.

The SR relation between signal-to-noise ratio (SNR) and noise for a neuron is given in Eq. 1. The SNR is 0 without added noise, rises quickly to a maximum peak with the addition of noise, and gradually decreases to 1 (\(D = \text{noise intensity}, \epsilon = \text{signal strength}, \Delta U = \text{threshold barrier height}\)) as noise overcomes the output

\[
\text{SNR} = \frac{(\epsilon \Delta U)^2}{\epsilon^2} e^{-\Delta U/D} \tag{1}
\]

Examples of this curve are presented in several of the later figures in this paper. SR has been found to have novel properties on larger numbers of elements. SR in an array of elements with a summed output generates an increased SNR to a broader range of noise (Chialvo et al. 1997; Collins et al. 1995), although this simulated finding was not found experimentally in cochlear nerves (Morse and Roper 2000). When the elements are coupled, as in array-enhanced SR (AESR), the signal detection improvement can vary depending on how the coupling is performed (Inchiosa and Bulsara 1995a,b; Kanamaru et al. 2001; Lindner et al. 1995; Locher et al. 1996). In this paper, we have chosen a coupling source to simulate electrical connections between closely neighboring cells (see METHODS). AESR has important implications in the nervous system, because it can make a neural network sensitive to a broad range of input signals when noise is present (Stocks and Mannella 2000).

Noise alone can produce oscillatory behavior in a single element under certain conditions, an effect closely related to SR (Gang et al. 1993; Lee et al. 1998). Another similar effect occurs in coupled arrays of neural models that are not presented with any periodic signal; they are able to respond with synchronous, near-periodic outputs when noise is added (Hu and Zhou 2000; Pham et al. 1998; Pradines et al. 1999; Wang et al. 2000). These effects have been called coherence resonance (CR) or autonomous SR. Throughout this work, CR is

Address for reprint requests: D. M. Durand, Dept. of Biomedical Engineering, Neural Engineering Center, Case Western Reserve University, CB Bolton Rm. 3510, 10900 Euclid Ave., Cleveland, OH 44106 (E-mail: dxd6@po.cwru.edu).

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used to describe only the case of a coupled network of neurons and autonomous SR that of a single neuron. In CR, the ability of noise to produce a synchronous, periodic response in the system is dependent on the noise characteristics and coupling between the neurons. When analyzed in the frequency domain, a sharp peak is produced as the system becomes more periodic, which can be used as a measure of synchrony. The synchrony follows a bell-shaped curve as noise intensity increases (Neiman et al. 1997).

While SR in a single element has been verified experimentally using several different models, experimental evidence demonstrating the presence or utility of AESR or CR in physiological neural systems is lacking. Although several different mathematical neural models have been used to investigate AESR and CR, even simultaneously (Lindner and Schimansky-Geier 1999, 2000), there has been little correlation of the effects with physiological parameters such as membrane dynamics, channels, and voltage. Rationalization and evaluation of the simulated data in light of its physiological ramifications has been difficult without these analyses or experimental verification. It is a major goal of this work to provide such correlations to physiological data by using a neural model that has been verified experimentally and that utilizes cellular parameters.

The beneficial effect of noise on signal detection has intriguing implications in the brain. Neurons such as CA1 pyramidal cells in the hippocampus are responsible for integration of signals from many different sources (Andersen 1990). Signal detection in these cells is complicated by the presence of noise (Bekkers et al. 1990; Destexhe and Paré 1999; Kamondi et al. 1998; Sawyer et al. 1989), the large number of synapses, and dendritic attenuation (Spruston et al. 1993), a situation that makes them ideal candidates for physiological SR (Stacey and Durand 2000, 2001). It is quite possible that AESR and CR also have physiological effects in the CA1 layer due to the network organization. The presence of these phenomena in the brain would have broad implications for normal signal detection as well as for abnormal detection such as epileptogenesis.

In this paper, we seek to analyze the effects of noise and coupling on signal detection in an array of simulated CA1 cells. This simulation is based on a detailed implementation of specific cellular parameters in CA1 cells (Warman et al. 1994) that have been verified experimentally (Stacey and Durand 2000, 2001). Noise and coupling have been added according to physiological conditions and have been carefully verified with experimental data. The model is used to test the hypothesis that noise and coupling can work synergistically to improve detection of a signal in the CA1 layer of the rat hippocampus through the effects of AESR and CR.

METHODS

Network simulation

An array of 10 simulated CA1 neurons previously described (Stacey and Durand 2000, 2001) was implemented using NEURON software (Hines 1993). The neurons (Fig. 1A) had membrane parameters derived from experimental data (Table 1) and were identical to each other. Each neuron contained an active soma with one sodium, one calcium, and four active potassium channels (Warman et al. 1994) as well as passive dendrites. Voltage data from the soma and current at the synapses were recorded separately with a sampling rate of 2,000 Hz.

Synaptic events generating the periodic input signal and random events were simulated using AMPA synapse functions (Destexhe et al. 1998). The amplitude of synaptic events was modulated by changing the maximum conductance ($g_{max}$) of the AMPA current. The periodic signal input was positioned on the distal branch of the apical dendrite of each cell and the amplitude adjusted to a subthreshold level (4 nS). The stimulus was a pulse train (Stacey and Durand 2000) of 2.5 Hz except where otherwise noted. At 2.5 Hz, the neurons were able to return to baseline between pulses to avoid any frequency-dependent effects of the signal. The signal was applied either to all neurons simultaneously ("global input") or to one neuron alone ("single input"; Fig. 1B). Noise was added to simulate any synaptic activity that is uncorrelated to the periodic signal. The noise was generated by 55 presynaptic axons, 10 of which contacted between three and nine different CA1 cells as en passant axons (e.g., Fig. 1C), while the remainder made independent connections. The en passant connections were generated randomly and did not cause any significant correlation among the CA1 cells. This connection scheme simulates the connectivity that exists in a rat hippocampal slice (Andersen 1990), where neighboring CA1 cells often receive the same presynaptic signal (Bernard and Whalen 1994).

Noise

Simulations were performed for two values of maximum conductance ($g_{max}$) at the noise synapses: 0.22 and 1 nS. These two values encompass the experimental range of miniature excitatory postsynaptic potentials (minis; $g_{max} = 0.21–1$ nS) (Bekkers and Stevens 1989; Destexhe et al. 1998; McBain and Dingleidine 1992; Stricker et al. 1996). Quantal size of random events were Poisson distributed (mean = 0.3). Noise variance ($D$, or noise intensity, in Eq. 1) was modulated by changing the mean firing frequency of the noise synapses. The firing of each presynaptic axon, which evoked a synaptic event, was calculated independently by comparing a threshold with a uniform random number generated at each time step (Stacey and Durand 2000). Changing this threshold thus changed the probability of firing at each time step. The characteristics of the synaptic noise current are shown in Fig. 2, which spans the entire range of noise simulated. Noise bandwidth and spectral power increased as expected with increased firing probability. Increasing $D$ increased the mean depolarizing current in a nearly linear fashion. The noise source had some low-pass filtering effects due to the frequency characteristics of the AMPA synapse, but they were present for much higher levels of $D$ than those used in these simulations. Also of note is the different response to noise with $g_{max} = 0.22$ nS versus 1 nS (see DISCUSSION). Noise was locally uncorrelated (Lindner et al. 1995) except the minor activity that exists in a rat hippocampal slice (Andersen 1990), where neighboring CA1 cells often receive the same presynaptic signal (Bernard and Whalen 1994).

Coupling

Coupling between each pair of cells was modeled as an additional voltage controlled current source ($I_{coupling}$) in the soma of each cell (Eq. 2). Current effects from all neighboring neurons were summed to produce a single current input at the soma

$$I_{coupling} = \sum_{j=0}^{N-1} c_{ij} (V_j - E_{max}) \quad (j \neq i) \quad (2)$$

$$f_c(c_i) = \frac{1}{C_{max}} \quad \text{all } c_i = c_j \quad (3)$$

The current amplitude was determined by the driving potential of the coupled neuron ($V_j - E_{max}$) and a coupling weight ($c_{ij}$). The coupling weight, $c_{ij}$, was bidirectional and randomly assigned from the uniform
interval \(0 \rightarrow C_{\text{max}}\), as shown by the probability density function in Eq. 3. In other words, each cell "i" received a coupling current from each of the nine cells "j", and the weight of coupling current was randomized on a scale determined by the value of \(C_{\text{max}}\). The coupling strength was multiplied by the arbitrary constant \(a\) to allow simple implementation in NEURON. The coupled current caused the potential to move in the same direction as the driving potential. This method produced an instantaneous change in somatic current that was dependent on the voltage change of another cell, which is similar to physiological forms of electrical coupling (see DISCUSSION). The distribution did not take into account any spatial effects suggested by the linear schematization in Fig. 1, B and C. The coupling mechanism did not generate any shunting between the cells that would diminish the signal strength (Lindner et al. 1995).

**Signal analysis**

The membrane voltages from all neurons were summed to produce a network voltage response: \(V_{\text{sum}} = \sum V_i\) (Collins et al. 1995). These data were mean-detrended \((V_{\text{sum(rest)}} = 0 \text{ mV})\) to remove the resting voltage contribution from each cell. Any subthreshold voltages \((V_{\text{sum}} \leq 70 \text{ mV})\) were then masked to a value of 0 while preserving the amplitude of suprathreshold responses. In this manner, the only non-zero data contained in the output was from action potentials and preserved their net amplitude above resting voltage to determine when multiple cells were firing. The resulting output time series was used to obtain the power spectrum (Wiesenfeld and Moss 1995) using the PSD function in Matlab (50,000-point Hanning window; 45,000-point overlap). The power at the input signal frequency (2.5 Hz) was divided by the baseband power (noise) in the region near 2.5 Hz to obtain the SNR. All data in this paper are averages of three independent simulations. The SNR obtained from each value of noise variance was plotted and used as data for fitting to the SR equation (Stacey and Durand 2000). In multiple-trace plots the SD is omitted from some traces for clarity, but in all cases the omitted deviations were comparable to those included in the figure and quite small. The values for \(\epsilon\) and \(\Delta U\) (Eq. 1) obtained from a least-square error fit were used to compare the SR responses.

For calculation of coherence, the output of a network presented

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**TABLE 1. CA1 model specifications**

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<tr>
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<table>
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<th>(\mu m)</th>
<th>Segments</th>
<th>(\lambda)</th>
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<td>400</td>
<td>10</td>
<td>0.443</td>
</tr>
<tr>
<td>Auxiliary 2° apical</td>
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<td>400</td>
<td>5</td>
<td>0.468</td>
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<tr>
<td>Main 2° apical</td>
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<td>400</td>
<td>5</td>
<td>0.828</td>
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Parameters for the CA1 model. The model architecture is identical to that in (Stacey and Durand 2000). The implementation differed in that noise variance was modulated by changing the mean frequency of firing.
with noise but no periodic signal was evaluated. The power spectrum of each simulation was computed as described above and then analyzed individually. Noise-induced synchrony appeared as a spike in the power spectrum. Synchrony from this resonant peak was measured using the coherence factor $\beta$ in Eq. 4, where $h$ is the height of the peak, $\omega_i$ is the frequency of the peak, and $\Delta\omega$ is the width at half-peak height (Gang et al. 1993)

$$\beta = h \cdot \omega_i / \Delta\omega$$  \hspace{1cm} (4)

**RESULTS**

The array of neurons was configured in four basic forms. First, the number of neurons in the network was varied without any coupling as the subthreshold signal and noise were presented to all neurons simultaneously. Second, with 10 neurons, coupling was varied as all neurons received the signal and noise again. These two configurations were designed to test the effect of varying coupling and the number of neurons on detection of a global signal. Third, the second simulation was repeated with signal removed from nine of the neurons. This configuration tested the ability of noise and coupling to affect recruitment of a network to a signal present at only one cell. Results were first obtained for these three configurations using noise with $g_{\text{max}} = 0.22$ nS and then repeated for 1 nS. Fourth, the signal was removed entirely and the 10-neuron network was presented with varying degrees of coupling and noise (0.22-nS source). This configuration was used to investigate oscillatory behavior that was present in many of the previous simulations.

**Effect of multiple uncoupled neurons on subthreshold signal detection**

The network was first used to test the effect of the number of detecting neurons on detection of subthreshold signals. Simulations with 1, 3, 5, and 10 neurons were configured with global inputs without coupling. Noise with mini-amplitude of 0.22 nS was applied. Several levels of noise variance were added to the system along with the subthreshold signal. The response shows that noise can improve the network's detection of the subthreshold signal (Fig. 3A). As the number of neurons increased, the amplitude of the response increased and detection of the input signal was improved (Fig. 3B). Increasing noise variance produced the typical SR curve and peak SNR increased as more cells were added (Fig. 3C). Addition of noise to the system produced peak SNR values of 174, 245, and 467 for 1, 3, and 10 cells, respectively. SNR for 5 cells were between those for 3 and 10 cells at all noise levels (data not shown). For variance $>$15 pA$^2$, the SNR was below the level predicted by SR. This was due to repetitive firing (oscillations) of the network present at high noise variance, which increased the background noise and will be discussed later. The center of the SR peak did not change with the number of neurons, but the amplitude varied with $N$. The change corresponded to an increasing value for the signal strength ($e$) in the SR equation (Eq. 1). These results show that arrays of uncoupled neurons, even as small as three, have an increased ability to improve detection of a global, subthreshold signal for low noise levels, but detection can be poorer than predicted by SR theory at high noise variance for noise with quantal amplitude on the low end of physiological range.

**Effect of coupling on signal detection**

The network was then used to test the effects of electrical coupling between cells when all neurons received the subthreshold input. Coupling was added and modulated between cells in the 10-neuron array with the same noise source as before. The network was tested with the global input configuration with four levels of $C_{\text{max}}$: 0, 0.1, 0.3, and 0.5. These levels were chosen to span a spectrum of physiological coupling. The maximum coupling ($c_{ij} = 0.5$) produced a 0.5-mV depolarization due to an action potential in a coupled cell, which was well within the physiological range (see DISCUSSION). The effect of different coupling levels on the network’s detection of a subthreshold signal in the presence of noise is shown in Fig. 4A. For noise (10.2 pA$^2$) that produced peak SNR, in the uncoupled network the signal was detected but the latency between the first and last cell to fire was often $>$20 ms (first trace). In the coupled network, there was a more coherent response: all 10 neurons tended to fire within a 10-ms span
Effect of noise and coupling on signal detection by a single neuron in a network

The simulation was then performed with the single input configuration (Fig. 1B) to test the hypothesis that a single cell can detect a subthreshold signal and recruit its neighboring cells through the combined effects of SR and coupling. Values of $C_{\text{max}} = 0, 0.1, 0.3, 0.5, 0.7, 0.9, 2.5,$ and $3$ were chosen to encompass all levels of physiological coupling in the system: from 0 coupling to 1:1 coupling of action potentials for $c_{ij} > 2.5$. The maximum depolarization without transmitting an action potential was 1.8 mV ($c_{ij} = 2.5$). Note that, due to randomization, the values of $c_{ij}$ for $C_{\text{max}} = 3$ were usually $<2.5$. This situation is representative of a single neuron receiving a signal surrounded by several quiescent neurons with a wide range of electrical coupling (see Discussion).

**SIGNAL DETECTION OF NETWORK WITH LOW NOISE VARIANCE.**

The network response to the single input at low noise levels is shown in Fig. 5A. For low-to-moderate coupling ($C_{\text{max}} = 0.9$), the network did not synchronize to the signal. The signal cell was the only cell able to detect the input at low noise levels. Increased coupling improved detection at the signal cell (Fig. 5A, first and second traces). The SNR plots (Fig. 5B) show that increased coupling shifted the SR curves up and to the left, corresponding to improved detection at these low noise levels. For comparison, the response of a lone cell to the same noise levels is included. These results show that even small coupling levels are able to improve a cell’s ability to detect a subthreshold signal in a noisy system through SR.

**SIGNAL DETECTION OF NETWORK WITH HIGH NOISE VARIANCE.**

Whereas the network’s improved sensitivity to noise was beneficial for low noise, it greatly diminished SNR at higher levels. Figure 5, C and D, shows that increased coupling produced oscillations that corrupt signal detection and depart from the SR equation. For all levels of coupling tested, the SNR was once more below the predicted SR value at high noise. An additional effect occurred independent of noise oscillations: the added noise from the nine other cells also decreased SNR. For this reason, detection with zero coupling was worse than for a single cell as noise increased. The driving cell is therefore able to use coupling to enhance its own signal detection at low noise, but is normally unable to overcome the additional noise and the oscillations to recruit the other cells.

**Effect of noise and coupling on recruitment in the network**

The same configuration was also examined for the ability of the single cell to recruit its neighbors to the subthreshold signal. Recruitment was defined as more than one cell firing in response to the input signal and producing an increased SNR. Under most circumstances, there was no significant recruitment in this network, as seen by the action potentials firing independently and the low SNR values in Fig. 5. As in the

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**Fig. 3.** Effect of number of cells in the network. **A**: top: raw data showing the trace of a single cell with a subthreshold signal. Bottom: input signal. When noise was applied, the signal was detected. **B**: raw data. As in A, there was no response before the addition of noise (data not shown). As the number of cells increased, there was a concurrent increase in both the number of action potentials in phase with the signal and random action potentials. However, the increased power in phase with the signal was stronger, leading to an improved signal-to-noise ratio (SNR). Note that the output was the sum of the array, so multiple concurrent action potentials appear as spikes >100 mV. Trace is for 5 s of data. **C**: effect of number of cells on signal detection. Data are fit to the stochastic resonance (SR) equation. Increasing the number of detecting elements changed the peak without changing the resonant center. All data strayed below SR theory at high noise. Bars indicate 1 SD for the 10-cell data. Comparable bars on the other data were removed for clarity.

(second trace). With high levels of noise (17 pA²), extraneous action potentials were generated, an effect worsened by increased coupling (third and fourth traces). Thus small levels of coupling and noise improved the signal detection, but as both increased the network fired clustered action potentials that overwhelmed the input signal. Results from 0.1 and 0.3 coupling levels (not shown) had a similar relationship, with values lying between the data shown for $C_{\text{max}} = 0$ and 0.5.

The SNR plots show the effect of coupling on signal detection (Fig. 4B). Coupling significantly increased the network sensitivity to noise, as shown by an increased SNR at lower noise levels and a sharper decline in SNR after peak detection. The peak SNR for maximum coupling ($C_{\text{max}} = 0.5$) was significantly higher than that with zero coupling (1.208 vs. 467) and occurred at lower noise (5.1 vs. 13.6 pA²). The coupling therefore caused a shift in the SR curve up and to the left (decreased $\Delta U$, increased $\epsilon$). However, with higher noise variance (17 pA²), the SNR was greatly decreased for higher coupling ($SNR = 7.3$ for $C_{\text{max}} = 0.5$ and 102 with $C_{\text{max}} = 0$) because the signal was overcome by the coherent oscillations. These results indicate that coupling can greatly affect signal detection and SR in the network. As the coupling rises, the network becomes increasingly more sensitive to noise—both to improve detection with low noise variance and hamper detection at higher variance.
previous simulation, noise from the other nine cells and oscillations prevented the cells from synchronizing to the input. There was only one combination of noise and coupling tested in which the 10 neurons synchronized to the input signal (Fig. 6, A and B). This occurred with high coupling ($C_{\text{max}} = 2.5$) and relatively low noise variance (1.36 pA$^2$). Interestingly, in this model, this noise level corresponds to the physiological baseline noise in a hippocampal slice (Sayer et al. 1989; Wahl et al. 1997). The neural array was very excitable at this combination of coupling and noise: it oscillated at about 2 Hz without a periodic signal present (Fig. 6, A, top trace). This response caused a low-amplitude, broad hump in the power spectrum centered at $\sim$2 Hz, whereas with addition of a 2.5-Hz signal, a sharp spectral peak appeared at exactly 2.5 Hz. It is important to note that signal frequency had no effect on signal detection in any simulation up to this point. Even when the periodic signal was raised above threshold, there was still no recruitment except at this specific combination (data not shown). Oscillations corrupted the signal frequency at the next noise level (Fig. 6A, third trace). Therefore in this network, a single neuron cannot recruit the other cells unless they are very excitable and prone to fire randomly near the input frequency.

The interesting ability of the periodic signal to recruit the excitable network was further investigated by using a 6-Hz input signal. This frequency was chosen after noting that the network oscillated near 5.8 Hz with 17 pA$^2$ noise and $C_{\text{max}} = 0.9$ without a periodic signal (Fig. 6, C and D). As predicted above, the 6-Hz signal was able to synchronize the network quite well. However, synchronization only occurred at the specific combination of coupling and noise, demonstrated by the unusual SNR plot. As with the prior example, the network was recruitable only when it was very excitable and prone to fire at a mean frequency just below that of the periodic driving signal. These results suggest that the network can be tuned to detect, or be recruited by, certain periodic signals by adjustment of coupling and noise.

**Effects of changing $g_{\text{max}}$ of the noise input**

The model was used to test the hypothesis that noise produced by minis of different quantal amplitude affects signal detection differently. The three preceding simulations were all repeated using noise mini amplitude of 1 nS. Because the mean amplitude of noise events was higher, lower frequencies were required to produce the same noise variance compared with 0.22-nS noise events (see DISCUSSION). There were differences noted for all three instances when compared with the lower amplitude simulations.

**CHANGING NUMBER OF UNCOUPLED NEURONS** Increasing the number of uncoupled detecting neurons increased the peak SNR with $N$ as in the previous case (Fig. 7A compared with 3C). However, compared with the 0.22-nS simulations, the improvement in signal detection was not as pronounced. The peak SNR was much smaller for 1 (13), 5 (79), and 10 (85) cells. In addition, more noise variance was necessary to reach peak detection, an effect that occurred for all simulations in this section (note different x axis scale in Fig. 7 compared to Figs. 3–6). However, the SNR to the right of the peak followed SR predictions more closely because the noise did not produce as many oscillations.

**CHANGING COUPLING IN 10 NEURONS** Increasing coupling with 10 neurons and a global input improved overall signal detection (Fig. 7B compare with 4B), but the effect was less pro-
nounced than with 0.22-nS minis. Again, the peak SNR was lower with 1-nS minis (162 for $C_{\text{max}} = 0.5$), and more noise variance was required to reach peak SNR. There was much less shift of the curve on both sides of the peak, showing that the sensitivity to both low and high levels of noise was not as pronounced.

**RECRUITMENT TO A SINGLE INPUT.** Ten coupled neurons and a single input cell were extremely sensitive to quantal size of the noise source. The network responded poorly to the single input under all circumstances—the SNR never exceeded 10, was maximal with 0 coupling, and had worse signal detection than a single cell (Fig. 7C, compare with Figs. 5, B and C, and 6B). The nine neighboring neurons were not recruited by the signal cell but rather began to fire in response to the noise. With large amplitude noise events, therefore, this system was unable to show any significant form of recruitment.

**High noise variance evokes an intrinsic frequency in a single cell**

In many simulations described above, high levels of noise produced SNR below the values estimated by the SR curve, particularly with noise generated by 0.22-nS minis. The diminished SNR was due to spontaneous, repetitive firing of neurons generated by the noise. A single neuron begins to fire repetitively when noise is raised above a certain threshold and the cell switches from Poisson-distributed shot noise (Bekkers and Stevens 1989; Brown et al. 1979; Cox and Lewis 1996) to near-periodic firing in a phase transition (Fig. 8). In this model...
using the 0.22-nS noise source, the phase transition occurred between 17 and 26 pA² noise variance and began at a frequency of ~4 Hz. This mean intrinsic frequency increased and became more discrete (a sharper spike in the frequency domain) with increasing noise variance. The response to a DC current is included for comparison. These results are similar to those found for autonomous SR in simpler neuron models (Gang et al. 1993; Lee et al. 1998). The physiological noise source in this model had a net depolarizing effect, but the neural response herein is comparable to previous work with zero mean noise (see DISCUSSION). No long-term accommodation effects occur because this model was designed to monitor detection of individual signals and did not include the effects of slower channels such as the afterhyperpolarization (AHP) potassium channel (Warman et al. 1994). This behavior of a single neuron plays an important role when large amounts of low-amplitude noise are present, especially when the neuron is coupled to other cells.

Noise and coupling contributions to bursting

The repetitive firing in a single cell was also present in the network and created oscillatory behavior at high noise levels. This effect was enhanced by coupling. The network was used to test the hypothesis that noise and electrical coupling combine to produce synchronous bursts similar to those generated by low calcium preparations (Perez Velasquez et al. 1994).

Ten cells were connected with various levels of coupling as noise (0.22-nS source) was added to the system with no periodic signal input. The network response for varying coupling and noise is shown in Fig. 9. With no coupling, all 10 cells fired asynchronously. For very small amounts of coupling ($C_{\text{max}} = 0.1$), the response was asynchronous for low noise (17 pA²), but increasing the noise (136 pA²) synchronized the network (Fig. 9A). This level of coupling is very small, producing ~0.01% change in neighboring cells (measured as $\Delta V_{\text{micell A}} / \Delta V_{\text{micell B}}$). For higher levels of coupling, even baseline noise

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**FIG. 6.** Recruitment of the excitable network with high coupling. A: raw data (2.5 coupling). Top: without signal, the network fired near 2 Hz. Middle: with signal added, the network became more periodic and fired at 2.5 Hz. Bottom: at higher noise levels, the network fired faster than 2.5 Hz. Traces are 5 s. Power spectra. Top: approximately 2 Hz firing. Middle: sharp peak at 2.5 Hz. Bottom: sharp peak at approximately 4.8 Hz. Signal frequency is buried in the noise. B: same data as Fig. 5, stressing disparity in response to 1.36 and 3.7 pA² noise with 2.5 coupling. These data could not be feasibly fit to the SR equation. SR fit for single cell (dotted line). SNR of data in bottom 2 traces of A (squares). C: raw data. Response to noise (17 nA²) without signal (top) and with 6-Hz signal (bottom) with $C_{\text{max}} = 0.9$. Trace is for 1.5 s of data. Power spectra. Top: mean frequency = 5.8 Hz. Bottom: frequency peak at 6 Hz. Input frequency of 6 Hz (arrow). D: SNR response to 6-Hz signal. The odd spike in 0.9 coupling occurs where the noise oscillations would be near 5.8 Hz. In this condition the network was tuned to detect a 6-Hz signal.
levels (1.7 pA^2) produced synchrony (Fig. 9B). The amount of synchrony (see Fig. 1D) for each combination of coupling and noise is shown in Fig. 9C. The maximum synchrony occurred for \( C_{\text{max}} = 2.5 \) (the highest simulated) for 170 pA^2. In all cases the synchrony dropped as noise increased beyond 170 pA^2. Burst frequency was dependent on noise variance but not coupling levels (Fig. 9D).

These results agree with previous simulations of CR (see discussion). Because of the physiological design of the simulation, these data also provide insight into the role that this form of CR can play in a true neural system. Analysis of the CR profile in light of physiology demonstrates two key conclusions about this system. First, the network will begin to synchronize and fire even at resting noise levels (1.7 pA^2) if coupling is increased sufficiently. A single cell will not fire at this noise level, requiring over 15 times higher noise variance to fire periodically in response to noise (26 pA^2, see Fig. 8). The coupling makes the system much more susceptible to noise.

**FIG. 7.** Effect of changing amplitude of noise events. A: effect of changing number of uncoupled detecting cells with 1-nS noise source (compare with Fig. 3). Data followed SR equation very well. Increasing \( N \) increased peak SNR. More noise variance was required to produce SR. B: effect of coupling on 10 cells and global signal source (compare with Fig. 4). SNR was improved for low noise and diminished at high noise with increasing coupling, although not as much as in Fig. 4. More noise variance was required for SR. C: SNR plot: inability of network to recruit (see Figs. 5 and 6). SNR <10 indicates inability to detect input well under any condition. Response of a single cell was better than all coupling levels. Data point for raw data (square). Raw data: data producing maximum SNR had multiple random action potentials from other 9 cells. Traces are 5 s.

oscillations, causing bursts even at baseline noise. Second, the network can produce similar synchrony for many combinations of coupling and noise. This phenomenon can be observed as the isosynchronous topological clines in Fig. 9, moving diagonally from high coupling/low noise to low coupling/high noise. Therefore a system with low coupling can potentially produce “high-coupled” synchrony merely by increasing the noise in the system.

**DISCUSSION**

**Choice of coupling mechanism**

Coupling between CA1 cells can take the form of synaptic connections or electrical coupling. Synaptic connections, which have large amplitude and measurable delay, are very sparse between CA1 neurons with a probability of connection of 1/130 (Bernard and Wheal 1994) and require very large networks to implement (Traub et al. 1999). In addition, they also include inhibitory connections, which would introduce an added degree of complexity and be difficult to treat as an intrinsic property of the system without more precise in vitro data. Electrical coupling can take the form of gap junctions or ephaptic interactions, both of which are basic components of the CA1 layer (Andrews et al. 1982; Jefferys 1995; MacVicar and Dudek 1981; Taylor and Dudek 1982; Vigmond et al. 1997). These two types of electrical coupling have quite similar effects. Both types allow bidirectional signals. The delay for ephaptic connections and gap junctions is very small (Traub et al. 1985). Both can also be involved in epileptiform activity when increased (Dudek et al. 1986; Jefferys 1994; Perez Velazquez and Carlen 2000). In the model presented here, both types were combined into a general, delay-free current source. The highest coupling levels simulated caused a depolarization of ~110 mV in response to an action potential in a coupled cell. This depolarization is comparable with previous recordings of electrical coupling (Taylor and Dudek 1982; Vigmond et al. 1997). High levels of coupling and noise evoked repetitive bursts of action potentials comparable with that in highly coupled epilepsy models (Jensen and Yaari 1997; Perez Velazquez et al. 1994; Schweitzer et al. 1992). Epileptiform activity has been linked to increased electrical coupling (Dudek et al. 1986; Jefferys 1994; Lee et al. 1995; Perez Velazquez and Carlen 2000). The normal physiological range of coupling is clearly below the level that causes constant bursting, but can be increased by effects such as osmolarity changes (Schwartzkroin et al. 1998), and low Ca$^{2+}$ (Bikson et al. 1999; Haas and
Jefferys 1984), which also have been used as models of epileptiform activity. Therefore electrical coupling strongly affects signal detection in CA1 cells and suggests a pathophysiological role of the effects shown in this paper.

**Noise characteristics affect stochastic resonance in neural networks**

Because of the time constant of neural membranes, the membrane voltage cannot return to baseline if signals arrive in quick succession. Noise produced by minis of lower amplitude (lower $g_{\text{max}}$) requires higher mean firing frequency to produce the same variance as higher amplitude minis, as shown in Fig. 2 and Eq. 5, which is based on the Poisson nature of the noise ($\sigma^2 = \text{variance}, A = \text{amplitude}, f = \text{mean frequency}$)

$$\sigma^2 \propto A^2 \cdot f$$  \hspace{1cm} (5)

Our data show that although similar variance can be produced with minis of disparate amplitudes, the neural response can vary significantly. There was a significant difference in the response to noise produced by minis with $g_{\text{max}} = 1$ and 0.22 nS, which encompasses the range of published baseline noise values (Bekkers et al. 1989; Destexhe et al. 1998; McBain and Dingledine 1992; Stricker et al. 1996). The simulations showed that 0.22-nS minis produced better signal detection (higher SNR, peak at lower amplitude variance with 1-nS minis) to the left of peak SNR and increased noise oscillations beyond peak SNR. As a comparison, the response to low-amplitude minis more closely approximates the response to a DC current: raising the voltage slightly changed the threshold for subthreshold signals and improved detection; raising it too much caused periodic firing. The response to higher amplitude minis, conversely, is more similar to coincidence detection: temporal summation of discrete synaptic events. SR is a useful tool that facilitates analysis of the system under both conditions. This effect stresses the importance of using models that address the frequency characteristics of neurons as well as carefully addressing the relationship between amplitude and frequency of noise events in SR analysis.

Noise in CA1 can vary significantly from baseline in size (Bekkers et al. 1990; Dobrunz and Stevens 1999; Larkman et al. 1997) and frequency (Destexhe and Paré 1999; Kamondi et al. 1998; Leung 1982). LTP can change both the amplitude and frequency in these cells is therefore larger than that simulated in this model. With an even larger range, it is clear that the neural response will depend greatly on the noise characteristics of the system. We conclude that it is important to evaluate the specific characteristics of noise presented to the cells rather than merely determine the internal noise variance. This conclusion has implications in the study of SR in neurons as well as in determining the characteristics leading to epileptiform bursting.

**Noise oscillations and bursting activity in a CA1 network**

When a single cell was presented with high levels of noise it fired periodically as in autonomous SR (Gang et al. 1993; Lee et al. 1998). When multiple cells were coupled, the network response was similar as the noise variance increased, ranging from shot noise to near-periodic firing typical of CR (Ha and Zhou 2000; Pham et al. 1998; Pradines et al. 1999; Wang et al. 2000). This result was previously detailed in more general mathematical models of neuronal networks (Kuramoto and Schulten 1984; Rappel and Karma 1996). It should be noted that although our results agree in all respects tested with previous work in CR, the noise source used herein was only excitatory and thus differed from previous CR work using zero mean noise. The effects of coupling on the frequency of oscillators have been known for some time (Kepler et al. 1990). Chaos has also been shown to decrease when comparable systems become more coherent and periodic (Molgedey et al. 1992). By analyzing the role of noise and coupling with a physiological model of hippocampal cells, these earlier mathematical analyses can now be applied to physiological situations.

The advantage of using this anatomic model is that it allows modulation of physiological sources that can be compared directly to experimental data. The input variance in Fig. 9C ranges from 1.7 to 510 pA$^2$. This range of synaptic current produced a somatic voltage variance of 14,000–42,000 $\mu$V$^2$. The low end is a good estimate of noise in a quiescent cell in the hippocampal slice (Wahl et al. 1997), but the higher value is 300 times greater than baseline and must be analyzed in view of the noise sources in CA1. We have previously described how the in vivo inputs that are not present in the slice can reasonably increase the background noise 300-fold (Stacey and Durand 2001). However, it is clear that this high level of noise would disrupt detection of all synaptic signals since all cells would be firing repetitively, insensitive to any other signal. Therefore these simulations deal with phenomena that would be expected to occur within the region of physiological noise levels.

The synchrony achieved with combinations of coupling and noise is a demonstration of a modified form of coherence resonance in a physiological model. It also produces synchronous, periodic bursting very similar to some models of epileptiform activity. With $C_{\text{max}} = 0$ the output was uncorrelated, but even small amounts of coupling produced some synchrony if the noise level was high. Synchrony also increased with coupling. Maximum synchrony occurred when coupling was highest and noise was near 170 pA$^2$ (Fig. 6C). This synergistic relationship provides a means by which small networks can reach synchrony for a wide range of coupling and noise. In a network where either noise or coupling is low, increasing the other parameter will increase synchrony. Even baseline noise (12,000 $\mu$V$^2$) or very small coupling ($C_{\text{max}} = 0.1$) can be brought to synchrony by this method. Conditions in which both coupling and noise increase simultaneously cause the greatest change. This finding agrees with experimental evidence that noise is increased before an epileptiform burst (McBain and Dingledine 1992) and also after stimulation (Manabe et al. 1992; Mennerick and Zorumski 1995) and coupling increases in some forms of epileptic activity (Dudek et al. 1986; Jefferys 1994; Perez Velazquez and Carlen 2000). CR in this physiological model therefore provides an interesting insight into the possible role of noise and coupling in the CNS: it is a simple model of epileptiform bursting. These results suggest that epileptiform activity can be evoked in a network by increasing excitability through a combination of increased noise and coupling that separately would not be sufficient to cause bursting.
Network contributions to signal detection

The network was configured to test two main hypotheses of signal detection. First, the effects of coupling and the number of cells on detection of a global signal were tested. With $C_{\text{max}} = 0$, the results are similar to the findings using the FitzHugh-Nagumo model (Collins et al. 1995) that showed the peak response increasing with $N$. However, the CA1 array did not respond to a broad, nonspecific range of noise variance. This is because oscillations at high variance and the limited ability of higher amplitude minis (1 nS) to improve detection both caused low SNR. It is possible that higher amplitude minis and larger $N$ would produce the broad response described by Collins et al. (1995) and Moss and Pei (1995), but the key issue is that physiological noise sources in CA1 cells cause oscillations and will corrupt detection in a manner not predicted by SR theory. When coupling increased, our results were only partially similar to previous coupled models for low noise levels—the peak resonance shifts up and to the left for increasing coupling (Inchiosa and Bulsara 1995a)—but deviated from those predicted by SR at high noise. A coupled network can therefore detect signals better than a single cell as long as noise does not induce periodic oscillations in the network. These results suggest that neural networks in the brain are able to utilize noise and coupling to improve detection under certain conditions. First, a network with more cells can detect a subthreshold signal with a higher SNR, leading to a stronger output. In the case of the CA1 cells, one functional consequence of this effect would be improved memory formation. Second, a highly coupled network is able to detect a signal further from threshold if noise is present. Functionally, such a network would be a sensitive detector. As suggested by Huber et al. (1999, 2000) for psychiatric illnesses, noise may play a major role in brain pathology as well. In this case, the network would also be prone to oscillations if noise rose too high and could become an epileptic focus. Obviously, these effects would have strong implications in both normal and pathological signal detection in the brain.

The second hypothesis was that a single cell could recruit other cells in the network through the combined effects of coupling and noise. With physiological noise sources, the signal cell was unable to recruit its neighbors under most circumstances. In most cases, the excitability of the other cells overwhelmed the input signal with random firing. Even a suprathereshold signal had poor recruiting ability, suggesting that recruitment in this network was difficult to produce using the chosen coupling mechanism regardless of signal strength. However, there were configurations in which the signal cell could recruit the other cells: when noise and coupling were high enough to bring the network near the phase transition to periodic firing. This is an interesting combination of the effects of CR and SR in the network. In these situations, a network prone to fire nearly synchronized bursts around a certain frequency could be driven to fire synchronously by a subthreshold periodic signal at slightly higher frequency. This CA1 network was specifically designed to ignore frequency effects in the signal by not including the potassium AHP channel or long-term potentiation (LTP) effects (Stacey and Durand 2000). However, this tuning phenomenon is frequency dependent and appears to be due to intrinsic membrane and network characteristics. This effect may provide a means for the network to be tuned to detect and fire at a specific frequency. Physiologically, this effect could be used by higher brain centers to tune CA1 or other coupled neurons to detect specific frequencies by merely changing the variance of presynaptic firing.

CONCLUSION

In summary, by using a CA1 model previously tested experimentally, we were able to construct a network, determine the effects of coupling and noise on signal detection, and relate the results to physiological data. The network showed large improvements in SNR as coupling and $N$ increased for noise near baseline, similar to other work in AESR. At high noise levels, the SNR did not match values predicted by SR due to periodic oscillations. These oscillations, as well as the specific characteristics of the SNR, were strongly dependent on the quantal amplitude of the noise, showing the importance of addressing this parameter rather than merely the overall variance. The highly coupled network was very sensitive to specific driving signals and was able to synchronize to them. Thus while SR does appear to be feasible under physiological conditions in this network, there are interesting deviations from SR theory that may have deep implications in the CNS. These results demonstrate the importance of relating neural AESR to physiological parameters to understand its possible role in vivo. CR in this model demonstrated the synergistic role of coupling and noise in making the network synchronize, and is a simple model of epileptiform activity as well as being the first demonstration of coherence resonance in a vigorous physiological neural model. These studies demonstrate interesting physiological implications of both coupling and noise on signal detection in the brain, using the framework of CR and AESR as investigative tools.

REFERENCES


