Synaptic Noise and Physiological Coupling Generate High Frequency Oscillations in a Hippocampal Computational Model

William C Stacey* (1,2)
Maciej T Lazarewicz (1)
Brian Litt (1,2)

1. Department of Bioengineering, University of Pennsylvania, Philadelphia, PA
2. Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA

* To whom correspondence should be addressed
ABSTRACT

There is great interest in the role of coherent oscillations in the brain. In some cases, high
frequency oscillations (HFOs) are integral to normal brain function, while at other times they are
implicated as markers of epileptic tissue. Mechanisms underlying HFO generation, especially in
abnormal tissue, are not well understood. Using a physiological computer model of
hippocampus, we investigate random synaptic activity (noise) as a potential initiator of HFOs.
We explore parameters necessary to produce these oscillations, and quantify the response using
the tools of Stochastic Resonance (SR) and Coherence Resonance (CR). As predicted by SR,
when noise was added to the network the model was able to detect a subthreshold periodic
signal. Addition of basket cell interneurons produced two novel SR effects: 1) improved signal
detection at low noise levels and 2) formation of coherent oscillations at high noise that were
entrained to harmonics of the signal frequency. The periodic signal was then removed in order
to study oscillations generated only by noise. The combined effects of network coupling and
synaptic noise produced coherent, periodic oscillations within the network, an example of CR.
Our results show that, under normal coupling conditions, synaptic noise was able to produce
gamma (30-100 Hz) frequency oscillations. Synaptic noise generated HFOs in the ripple range
(100-200 Hz) when the network had parameters similar to pathological findings in epilepsy:
increased gap junction or recurrent synaptic connections, loss of inhibitory interneurons such as
basket cells, and increased synaptic noise. The model parameters that generated these effects are
comparable with published experimental data. We propose that increased synaptic noise and
physiological coupling mechanisms are sufficient to generate gamma oscillations, and that
pathologic changes in noise and coupling similar to those in epilepsy can produce abnormal
ripples.
INTRODUCTION

High Frequency Oscillations

Since the early 1990’s, several groups have evaluated fast coherent oscillations in the brain (Huang and White 1989; Allen, Fish et al. 1992; Buzsaki, Horvath et al. 1992; Fisher, Webber et al. 1992; Ylinen, Bragin et al. 1995; Chrobak and Buzsaki 1996; Bragin, Engel et al. 1999; Csicsvari, Hirase et al. 1999a). There are several patterns of these High Frequency Oscillations (HFOs) seen in different regions of the brain. The term “HFOs” is used to describe a number of possibly disparate phenomena, seen in both normal and pathologic circumstances. Even less standardized is what frequency range actually constitutes an HFO—the term has been used to describe activity anywhere from 60 (Worrell, Parish et al. 2004) to 700 (Amassian and Stewart 2003) Hz. From a clinical neurophysiology point of view, the term refers to activity beyond the typical range of EEG recordings, which historically have a 70 Hz cutoff frequency. HFOs have been recorded in normal human neocortex, both on somatosensory evoked potentials (Coppola, Vandenheede et al. 2005) as well as on EEG’s (Gonzalez, Grave de Peralta et al. 2006). HFOs in the fast gamma range (60-100 Hz) have been associated with epilepsy, particularly in the preictal period (Traub 2003; Worrell, Parish et al. 2004), though they are also seen in normal conditions (Whittington, Traub et al. 1997). Because the exact boundaries are not standardized, it is necessary to clarify the usage of these terms in the present work: “gamma” will refer to frequencies from 26-100 Hz; “ripples” from 100-200 Hz; and “fast ripples” > 200 Hz. Gamma oscillations that have been associated with epilepsy are further subdivided into the “fast gamma” range (60-100 Hz), while those below 60 Hz are likely normal. “HFO” refers collectively to any frequency above 60 Hz (fast gamma, ripples, and fast ripples), which may or may not be pathological.
There has been considerable work describing how the physiological network of pyramidal cells and interneurons interact to form coherent oscillations. Basket cell inhibition is a well-known phenomenon in both hippocampus and neocortex, and a key component of many theories of HFO generation (Amitai, Gibson et al. 2002; Bibbig, Traub et al. 2002; Klausberger, Magill et al. 2003; Traub, Contreras et al. 2005a; Le Van Quyen, Bragin et al. 2008). Coherent oscillations in neuronal networks are produced when coupled interneurons generate rhythmic inhibition to large numbers of pyramidal cells, which in turn feedback to the interneurons (Traub, Whittington et al. 1996b; Traub, Jefferys et al. 1997; Borgers, Epstein et al. 2005). This phenomenon, known as Pyramidal Interneuron Network Gamma (PING), forms a periodic oscillation with a frequency that is dependent upon the feedback delay as well as the drive to the pyramidal cells (Traub, Bibbig et al. 2000). Computational models of gamma oscillations often utilize direct current injection into pyramidal cells as the driving force (Traub, Whittington et al. 1996b; Tort, Rotstein et al. 2007). However, it has been difficult to reproduce higher frequency oscillations (>100 Hz) with those PING mechanisms, which has led to other theories such as driving from ectopic spikes generated in pyramidal cell axons which are coupled to form an axonal network by axo-axonic gap junctions (Draguhn, Traub et al. 1998; Traub, Contreras et al. 2005b).

One subgroup of HFOs, known as ripples, generally refers to oscillations occurring at about 100-200 Hz (Bragin, Engel et al. 1999). Ripples have been used to describe both abnormal activity associated with epileptiform sharp waves (Bragin, Wilson et al. 2004) and normal behaviors such as physiological sharp waves (Ylinen, Bragin et al. 1995) and memory consolidation (Buzsaki, Horvath et al. 1992; Csicsvari, Hirase et al. 1999a; Foster and Wilson 2006; O'Neill, Senior et al. 2006). In some areas, such as the hippocampal dentate gyrus, they
are a marker of epileptic tissue and may be formed in a different manner (Engel, Bragin et al. 2009) than “normal” brain oscillations (Sejnowski and Paulsen 2006). Ripples appear to require fast coupling between pyramidal cells, such as axonal gap junctions or ephaptic connections (Draguhn, Traub et al. 1998; Fox, Bikson et al. 2004; Traub, Contreras et al. 2005b). Another subset of HFOs, named “fast ripples” by Bragin et al., are comprised of oscillations from 250-500 Hz, and are proposed as a biomarker of epileptic tissue (Bragin, Engel et al. 1999; Staba, Frighetto et al. 2007; Jacobs, Levan et al. 2009; Jacobs, Zelmann et al. 2009). Fast ripples are only recently being mechanistically classified (Foffani, Uzcategui et al. 2007), and there is much interest in describing how they are formed, specifically in epileptic tissue (Engel, Bragin et al. 2009). The mechanisms that generate HFOs are less understood for ripples and fast ripples, owing in part to the difficulty posed by recording them and distinguishing HFOs from ensembles of thousands of individual neurons firing at such high frequency. Below we explore a method by which HFOs can be generated using conventional coupling mechanisms with the only driving force being random synaptic activity. We relate these findings with changes seen in epilepsy, showing in particular that ripples can be produced when the model has pathological changes that are similar to those in epileptic tissue.

**Stochastic Resonance and Coherence Resonance**

Stochastic resonance (SR) was first described over 20 years ago as a method of explaining how detection of a subthreshold signal can be improved by the presence of random noise (Benzi, Sutera et al. 1983; Fauve and Heslot 1983; Moss, Ward et al. 2004). Originally described in nonlinear systems from geology and physics, it was later noted to play a role in neural signal detection, both in peripheral and central systems (Bulsara, Jacobs et al. 1991; Douglass, Wilkens et al. 1993; Collins, Imhoff et al. 1996; Gluckman, Netoff et al. 1996; Levin...
and Miller 1996; Stacey and Durand 2000; Stacey and Durand 2001; Stacey and Durand 2002).

Later studies further established the potential uses of this method in physiological signal
detection (Fallon, Carr et al. 2004; Fallon and Morgan 2005; Hong, Martin et al. 2006; Lugo,
Doti et al. 2008) and information processing in the hippocampus (Yoshida, Hayashi et al. 2002).

These studies demonstrated that certain levels of noise are able to improve detection of
subthreshold signals in the nervous system, which has intriguing biological implications for both
the role of noise and for the mechanics of neural signal detection.

Further SR research explored the effects of having multiple detectors, known as Array
Enhanced SR (Lindner, Meadows et al. 1995), which predicted that the signal to noise ratio of a
single detector would improve proportionally with the number of neighbors to which it was
coupled. This latter system is more suitable to describe physiological neural systems—
individual neurons nearly always exist in arrays, especially in the central nervous system, and
there are varying degrees of direct and indirect coupling within the array. Once neurons become
coupled in their output behavior, however, another related effect of noise is formed, Coherence
Resonance (CR, also known as Stochastic Coherence). CR is a phenomenon from the physics
field that describes how a network of coupled detectors can produce a coherent, nearly-periodic
output when presented with random noise inputs (Rappel and Karma 1996; Neiman, Saparin et
al. 1997; Pham, Pakdaman et al. 1998; Pradines, Osipov et al. 1999; Hu and Zhou 2000; Wang,
Chik et al. 2000). Computational models of neural networks have been shown to produce this
activity as well (Lindner and Schimansky-Geier 1999; Stacey and Durand 2002; Chiu and
Bardakjian 2004; Balenzuela and Garcia-Ojalvo 2005).

Since pyramidal cells in the brain have a tremendous number of synaptic inputs, they
experience a broad range of synaptic activity. This activity is a combination of random release
of neurotransmitter (minis), and the summation of sometimes thousands of independent synaptic signals from various brain areas. At times the synaptic activity can become very intense, such as during active cortical states (see Discussion), and can produce a significant amount of postsynaptic activity. SR and CR allow the researcher to designate a specific input as the "signal" (in the case of SR), while all other independent inputs can be treated as "noise" (Stacey and Durand 2002). Using this approach, Stacey and Durand demonstrated that oscillatory neural activity can be produced by physiologically-feasible levels of noise and coupling. In the present study we use a more detailed computational model of hippocampus to explore parameters necessary to produce HFOs, and quantify the response using the tools of SR and CR. In order to facilitate this analysis, throughout this manuscript all random synaptic activity is classified and referred to as “noise.” Using this method, the coherence, frequency, and signal-to-noise ratio (SNR) can be quantified and compared across trials. The results are compared with other physical models of SR and CR, and the parameters are compared with experimental data. Using this analysis, we demonstrate a method by which physiological inputs and coupling can produce coherent oscillations, and create pathologic changes similar to epilepsy.

METHODS

Computer model

A reduced physiological model of the hippocampus was adapted from (Tort, Rotstein et al. 2007). All simulations were performed in NEURON 6.1 on a PC computer (Hines and Carnevale 1997). Our adaptation was performed to evaluate transient high frequency events, rather than slow theta oscillations, so OLM cells were removed and only one module was simulated (the previous model contained 4 modules connected by OLM cells). Each module
contained 80 pyramidal cells and 20 basket cells (Fig. 1). Pyramidal cells had 5 compartments
(basal dendrite, soma, and 3-segment apical dendrite) and contained current sources from the
following ion channels: sodium $I_{Na}$, A-type potassium $I_{Ka}$, delayed-rectifier potassium $I_{Kdr}$, and
non-inactivating, nonspecific cation $I_h$. Basket cells contained one compartment with $I_{Na}$ and $I_{Kdr}$,
(with different parameters from pyramidal cells, as described in (Tort, Rotstein et al. 2007)). The
basket cells were connected efferently all-to-all with the pyramidal cells using inhibitory GABA
synapses. Each basket cell also received afferent excitatory (AMPA) synapses from 10
randomly selected pyramidal cells. One simulation was performed in which these pyramidal-to-
basket cell AMPA synapses had a component of NMDA current. For all synapses, synaptic
strength was modulated by changing the conductance, which in the model represents the density
of channels and affects the amplitude of the postsynaptic current. Thus, a doubling the
conductance doubled the amplitude of the current function, and a connection could be “removed”
by setting conductance to 0. When NMDA current was added, it was an additional current with
peak conductance specified as a ratio of the peak AMPA conductance ($G_{\text{max(NMDA)}} = \text{ratio} \times
G_{\text{max(AMPA)}}$). All synaptic, channel, and membrane parameters were essentially unchanged from
the published model, and are also similar to another physiologically-based hippocampal model
(Traub, Jefferys et al. 1997). Additional alterations to the model were: 1) addition of
independent, excitatory AMPA synapses on each basket cell and on midpoint of the proximal
apical dendrite of each pyramidal cell as “noise synapses”; 2) optional gap junctions between
pyramidal cells or between basket cells based on the implementation in (Traub, Contreras et al.
2005a); 3) addition of optional recurrent AMPA synapses in pyramidal cells (see below). For
simulations testing detection of subthreshold signals, a 16 Hz signal was input at the first apical
dendrite segment (A1) of the pyramidal cells. Noise synapses were used to introduce
independent synaptic “noise” events by determining at each 0.5 ms time step whether a random
number generator (uniform distribution) was above a threshold. The threshold was the same for
each cell of the same type, and was varied to produce the different noise intensities. The quantal
size of the synaptic event was further randomized using a Poisson distributed weight
(lambda=0.8; method identical to that in (Stacey and Durand 2000)). Gap junctions were
represented as instantaneous current injection, based on the voltage difference between the cell
compartment through an assigned conductance, using the “halfgap.mod” format in NEURON.
Gap junctions between basket cells were soma-soma, and in the pyramidal cells were between
proximal apical dendrites (A1-A1). Recurrent AMPA synapses were simulated as independent
AMPA synapses on the A1 segment triggered by somatic action potentials, with very short (0.1
ms) delay. Each of these changes was used at different times during the acquisition, as described
in the Results section.

Data Processing

The output of the network was generated as the average of all pyramidal cell somatic
voltages. Thus, in the output an action potential (AP) in one cell generated a waveform that was
1/80 the amplitude of a single AP, making a waveform that was roughly 1 mV. Coincident APs
produced higher amplitude output, while slight differences in onset time resulted in widening of
the output waveform due to jitter. The summed output was then analyzed by computing the
power spectral density using the PWELCH function in Matlab (Mathworks, 2008). Note that
this function inherently averages the result over multiple time windows. Most data were
generated for 1 second duration in order to provide a large number of sample windows for averaging.

**SR analysis:** The signal to noise ratio (SNR) was calculated by dividing the power at the input frequency by the average power near that frequency, in the manner commonly used for SR (Moss, Ward et al. 2004) (see Fig. 2B). The SNR at each noise intensity was then plotted and compared with a representative SR curve (equation 1: \( \varepsilon = \) signal strength; \( \Delta U = \) barrier height, \( D = \) noise intensity).

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

**CR analysis:** Coherence (\( \beta \)) is based on the same SNR calculation used in SR, adjusted for frequency and peak width. It is computed as shown in equation 2 (\( \omega_p = \) frequency producing maximum spectral power, \( \Delta \omega = \) width at half-peak height, \( h = \) SNR of peak as described for SR).

The coherence was then plotted as a function of both input noise intensity and coupling.

\[
\beta = h \times \frac{\omega_p}{\Delta \omega}
\]

**Noise analysis:** Noise intensity was calculated by recording the input noise current at the AMPA noise synapse for each noise threshold level (see above). The second moment of this current about its baseline was then calculated. Since the baseline current was 0 before noise began, the value was the current squared (Eq. 3). This method is similar to calculating the variance but includes the DC offset of the current, and thus is more plausible as the total physiological synaptic input.

\[
\text{Noise intensity} = (I_{\text{noise synapse}})^2
\]

RESULTS
Stochastic Resonance: noise improves detection of subthreshold signal

The network was first configured to evaluate how SR affected its signal detection. This model incorporated inhibitory interneurons, a physiological system element that has not been included in previous models of SR. The input signal was configured as a subthreshold synapse that contacted pyramidal cells on the A1 segment. When contacting multiple cells, the signal arrived simultaneously on each postsynaptic cell, simulating a single branched afferent axon contacting the apical dendrite with multiple synaptic contacts. The signal was generated as a 16 Hz periodic synaptic event, a frequency chosen to avoid complex dynamics caused by the cells’ natural resonance near 20 and 40 Hz. Noise was generated as random AMPA synaptic events at the noise synapses described above. For the remainder of this work, “noise” will refer to these random excitatory synaptic events.

Single cell

A single pyramidal cell was presented with a subthreshold AMPA signal and synaptic noise (Fig. 2). When the subthreshold signal was presented alone (2A, top), the cell had subthreshold depolarizations but never fired an action potential. Random synaptic activity alone caused the baseline membrane voltage to fluctuate (2A, bottom). Each level of noise produced a mean depolarization of the cell, which could produce spontaneous action potentials. For lower levels of noise, there were only rare, lone action potentials: Poisson firing. As noise intensity increased, the mean depolarization increased asymptotically. At 0.008 nA$^2$, the depolarization was 12 mV with a variance of 149 mV$^2$, and the cell fired frequent action potentials at random intervals (mean firing rate < 10 Hz). At 0.01 nA$^2$ and beyond, the noise produced spontaneous, nearly periodic action potentials. The periodicity became more pronounced as the noise intensity increased. This activity will henceforth be referred to as “noise oscillations.”
When both noise and signal were presented to the cell, the cell exhibited SR. The simulation was performed for a noise intensity ranging from 0 to 0.03 nA$^2$. By definition, as there are no action potentials without any added noise (subthreshold signal), the SNR is 0. Thus, in all cases of SR (Figs. 2,3,4), SNR is zero for zero noise. For low noise ($< 0.005$ nA$^2$), signal detection was improved as the cell began to fire in response to the signal input, as seen in Fig. 2A, second line. For higher noise, the cell began to fire in response to the noise itself, producing extraneous action potentials (2A, line 3). SR analysis of the raw data quantified this response: the SNR rose for low noise levels then decayed as the noise increased (Fig. 2B). The full response to the noise range is shown in Fig. 2D. In this case, the data do not fit very well with the SR curve at higher noise levels due to the noise oscillations, which are not addressed in SR theory (Stacey and Durand 2002). The sample SR curve shown in 2D is the typical shape of the SR curve, and does not fit the data well. In the following figures (Figs 3,4), when the parameters in Eq. 1 attempted to fit to the data, they yielded unusually-shaped SR curves due to the lower SNR at high noise levels. The pyramidal cell was then connected to a single basket cell, which had GABA conductance equal to that of 20 basket cells. The inhibitory input presented to this cell was thus of the same magnitude as in individual cells in the full network, where 20 separate basket cells contact each pyramidal cell. Adding basket cell inhibition actually improved signal detection: the basket cell effectively inhibited many of the noise-induced action potentials (Fig. 2C), which led to a significantly-higher SNR (2D). Beyond 0.01 nA$^2$, however, the noise oscillations again disrupted SNR despite the basket cell inhibition.

**Entire network**

All 80 pyramidal cells and 20 basket cells were then implemented to test signal detection in the full network. The 16 Hz input signal was input to 20 pyramidal cells, with each cell
receiving the synaptic event at the same time. These 20 “signaled” cells had no direct
connections with any of the other pyramidal cells, only the indirect feedback provided through
the basket cell connections. As with a single cell (Fig. 2), noise was able to improve detection of
the subthreshold signal. In order to demonstrate the network activity, spike raster plots are
presented in Fig. 3A. These plots show firing times of all basket and pyramidal cells. The SNR
analysis (3B, 3C) is identical to the previous figure, though the range of noise tested was much
larger. The 20 signaled cells were arranged as 4 groups of 5 cells, and are the only cells firing
with low noise (3A, left). As the noise increased, many other cells began to fire and the SNR
decreased. For many intermediate amounts of noise (3A, middle), the SNR was low because the
network fired at harmonics of the signal (see next paragraph). With very high noise levels (3A,
right), the noise was high enough to overwhelm the 16 Hz signal, and the network was extremely
active, and it tended to oscillate coherently at a separate frequency (see next section). The SNR
plot (3C) again demonstrates that signal detection was improved at low noise as predicted by SR,
but deviated at higher noise levels due to noise oscillations, which led to the unusually shaped
SR curve.

The network output was then compared with simulations in which there were no basket
cells (Fig. 4). Without basket cells, there was increased, uninhibited noise from the pyramidal
cells not receiving the signal, and the total noise was increased. Therefore, despite the input
signal being visible in the raw voltage, the SNR of the 16 Hz signal was greatly reduced. As
seen in the spike rastergrams in Fig. 4A, the basket cells reduced the total amount of noise, and
also produced periods of relative inhibition immediately after each signal event. The basket cells
clearly improved the SNR of the subthreshold signal in the presence of noise. In addition, they
produced a global periodic synchronizing feedback, which often promoted firing of the
unsigned cells at the same frequency (though often with phase delay). The result was that, through basket cell connections, a periodic signal received by some members of the network was able to tune the output of the entire network. This entrainment to the input signal frequency or its harmonics is demonstrated in Fig. 4C, in which the addition of a periodic input effectively quantized the output frequency of the network containing basket cells (20 signaled cells, intact basket cells; conditions identical to those in Fig. 3 and solid triangles in Fig. 4B). Both the improved SNR and frequency entrainment were more pronounced with larger numbers of signaled cells. Additional simulations in which there was only a single signaled cell (Fig. 4B, hollow squares) and 4 signaled cells (not shown) demonstrated a dose-response, in which SNR was higher with increased numbers of signaled cells. The overall result was improved SNR with basket cells present, showing that inhibitory feedback was able to improve signal detection.

As expected for array enhanced SR, the response of the ensemble improved with an increasing number of signaled elements. These results, however, are quite different from previously-reported examples of SR and AESR. First, noise oscillations disrupted signal detection for higher noise levels, deviating from the predictions of SR. Second, signal detection was improved with purely inhibitory feedback, which effectively decreased the noise content at low noise levels and raised SNR. Lastly, the basket cells entrained the network to fire at specific frequencies, which were often strongly influenced by the subthreshold periodic signal. These last two effects of basket cells wielded a powerful influence on the network output. At very high noise levels, the basket cells also had a role in synchronizing the network to noise oscillations, as seen in Fig. 3 for 0.06 nA². The generation of network oscillations is explored in further detail in the next section, but for purposes of SR it produced “noise” that quickly overwhelmed detection of the deterministic signal input.
Coherence Resonance

The ability of a noisy input to produce coherent, nearly-periodic oscillations in a coupled network is the basis of CR. As in previous simulations evaluating SR in pyramidal cell networks (Stacey and Durand 2002), noise oscillations were prominent in the current model and disrupted the expected SR curve, even for small amounts of noise. That effect was best seen in Fig. 3 for 0.06 nA² noise, where the noise oscillations completely overwhelmed the input signal. The network effectively produced a coherent, periodic signal with no input other than random noise. The rest of the simulations were performed with noise as the only inputs in order to explore the role of CR in this model.

Oscillations in a single cell

The network oscillations result from coupling of individual oscillating neurons. The model was first tested with a single neuron in order to compare it with the network response. High noise levels presented to a single pyramidal cell produced noise oscillations that reached a maximum of 190 Hz (Supplemental Figure 1). Connecting the single neuron to a basket cell lowered the peak frequency slightly in proportion to the synaptic strength. These results in a single cell reinforce two important concepts: that random noise can produce a nearly-periodic output in a neuron, and that basket cells can modulate the frequency response.

Network oscillations with basket cell coupling

In a network of oscillating uncoupled cells, each oscillates independently and the output is not coherent (e.g. see Fig. 4A, right, when basket cell coupling is removed). With sufficient coupling, oscillating neurons can become synchronized. CR provides a method for quantifying and analyzing this effect. The network was first connected in its baseline configuration, with no
coupling except for the basket cells. Fig. 5 demonstrates that noise and coupling synergistically generated coherent oscillations in the network. CR is typically characterized by low coherence at lower noise levels, a “resonant” peak of coherence as noise increases, followed by a drop at very high noise levels as the network desynchronizes (Stacey and Durand 2002). Furthermore, coherence increases as coupling strength is increased. CR analysis, therefore, computes the coherence as both noise and coupling are modulated. Fig. 5A shows raw data (spike rasters and voltage output) for the network with basket cell coupling of 0.275 nS and three noise levels. This coupling corresponds to the baseline conductance of the GABA synapse from the basket cells to pyramidal cells. For each noise level, the network oscillated at different frequencies (20, 36, and 69 Hz, respectively). When the cells fired very synchronously, as for 0.06 nA², the PSD peak was very sharp, and the coherence was higher. That the peak coherence occurred at 36 Hz is not surprising, as it corresponds to the frequency expected with the PING mechanism involving GABA synaptic feedback from the basket cells.

The coherence for a broad range of noise and coupling intensities is shown in Fig. 5B. Coherence rose with increased coupling, and the resonant peak was present as noise intensity increased. There were, however, two important differences from standard CR theory. First, unlike typical CR systems, the coupling herein is purely inhibitory, through GABAergic synapses, whereas CR is normally described in positive feedback systems. Second, the data differ significantly from the expected CR curve at high noise levels: after an initial drop in coherence at high noise, the coherence increases relentlessly thereafter. This deviation from CR theory is due to the characteristics of this neural system. The pyramidal cell firing rate is much slower than the maximum basket cell firing rate, so even at high noise levels the inhibitory coupling on the pyramidal cells is sustained, whereas in typical CR the noise would overcome
the coupling at high levels and lower the coherence. In addition, the postsynaptic membrane effectively filters high frequency signals, and at very high levels noise resembles a DC current. For comparison, the response of the network without any basket cell connections is also shown in Fig. 5 B, C (0 nS), demonstrating that without coupling there is some inherent synchrony generated at high noise when all the cells fire at nearly the same rate, even though at low noise there is no CR peak. These high levels of noise, however, are likely at the extreme of normal physiology (mean rate of noise events for noise above 0.2 nA^2 is > 4000 Hz).

The frequency of the coherent oscillations is of particular interest (Fig. 5C). This model was originally designed to simulate activity of the hippocampus, specifically how basket cell feedback can produce gamma oscillations when the pyramidal cells received DC current injection (Tort, Rotstein et al. 2007). These results show that random synaptic inputs can also generate gamma oscillations (>30 Hz), reaching up to the HFO range (110 Hz with the baseline 0.275 nS coupling). The oscillation frequency rose proportionally higher as synaptic strength from the basket cells decreased. With very low basket cell input (0.075 nS), the frequency reached nearly 150 Hz. These frequencies are significantly lower than in a single cell (190 Hz), even one with feedback from 20 basket cells (175 Hz, Supplemental Figure 1). Thus, the oscillation frequency decreased when there were more pyramidal cells and more basket cell input.

**Effect of NMDA current on gamma power**

Recent experimental work has demonstrated that NMDA blockade (with ketamine or MK-801) results in increased gamma frequencies in rat neocortex (Pinault 2008) and hippocampus (Lazarewicz, Ehrlichman et al. 2009). The above simulations were repeated with varying levels of NMDA current added to the pyramidal-to-basket cell “AMPA synapse” to test
this effect. All other parameters were unchanged; the simulations were performed using the
same range of pyramidal cell noise as in Fig. 5, with the baseline level of GABA conductance
(0.275 nS). Several levels of NMDA current were tested, generated with a peak conductance that
was a specified ratio of the AMPA current ranging from zero to 0.5. The results, shown in
Supplemental Figure 2, demonstrate that increasing amounts of NMDA current decreased the
coherence, the peak oscillation frequency, and the total gamma (30-100 Hz) power in the
network. Peak oscillation frequency was more sensitive to NMDA current at high noise levels
(>0.11 nA², Suppl. Fig. 2 D). The difference in gamma power was very pronounced for all
levels of noise (Suppl. Fig. 2 E). With high NMDA current (ratio 0.1 and above), the network
was suppressed and did not produce oscillations. These results agree with the experimental
finding that increasing NMDA blockade increases the gamma power. They also provide a
possible explanation for this phenomenon: the additional NMDA current caused the basket cells
to fire more frequently, and produced increased inhibitory feedback on the pyramidal cells that
lowered their firing rate. Effectively, increasing NMDA current alters the dynamics of PING
and decreases the gamma power. The remainder of the simulations did not include any NMDA
current.

**Coherent oscillations with gap junctions**

Gap junctions provide an alternative method for generating coherent oscillations. Gap
junction current was generated according to Eq. 4, where \( I_{\text{gap}} \) is in nA, voltages in mV, and \( V_{\text{gap}} \)
is assigned as the \( V_m \) of the connected cell. The conductances were tested within a broad range,
from a “low” level causing minimal change to a “high” level where connected cells always fired
synchronously.

\[
I_{\text{gap}} = (V_{\text{gap}} - V_m) \times g_{\text{gap}} \tag{4}
\]
All of the previous CR simulations were repeated with gap junctions between basket cells, using low (1e-5 μS) and high (1e-4 μS) conductances. Basket cells can be highly coupled by gap junctions (Fukuda, Kosaka et al. 2006), forming wide-ranging connections (Sik, Penttonen et al. 1995), which was an important part of the results of the original implementation of this model in (Tort, Rotstein et al. 2007). When measuring the output of the network (pyramidal cell membrane voltage), there was no appreciable change in either the coherence or the frequency response when the gap junctions were present in the basket cells (data not shown). However, when noise was added directly to the basket cells, gap junctions had significant effects on the network (see later section).

Gap junctions were then placed between pyramidal cells. Unlike the basket cells, pyramidal cells are not so tightly coupled as basket cells in vivo, as evidenced by their independent firing. Little data about the prevalence and strength of these connections is available, but they are present to varying degrees. The simulation was performed for several levels of coupling between 0.001 μS and 0.05 μS (which produced the low and high levels as above), with the connection in the A1 dendrite segment of each cell. Two protocols were tested. First, a total of 39 scattered connections were made between the 80 cells. This left many of the cells without any connections, and created several clusters of coupled cells. The coherence was reduced in this situation from when there were no gap junctions. This happened because the clusters and the uninvolved cells were all independent, often oscillating at different frequency or phase. An example is shown in Fig. 6A, which shows that even with very high coupling (0.05 μS) the overall coherence was actually lower than the corresponding simulation without any gap junctions (2200 vs. 13800 in Fig. 5). Although the cells connected by gap junctions were synchronized, the overall ensemble was not, and the output was disrupted by the uncoupled cells.
This low number of gap junction connections never produced greater coherence than when basket cells were the only coupling mechanism. When basket cells were removed, the coherence was very poor due to increased noise (not shown).

In order for gap junctions to have a significant effect in this model, they had to be widely distributed. At the extreme, all cells would be connected in a syncytium. To simulate this, all pyramidal cells were coupled in a linear “inline” chain with 79 gap junctions (1-2-3-…-78-79-80). These gap junctions had strong effects on the coherent oscillations. One interesting change was the loss of the “resonant peak”: there was no drop in coherence for noise 0.1 – 0.15 nA² with higher levels of coupling (Fig. 6B, solid line is baseline data from Fig. 5 for comparison).

Another major difference was the increased oscillation frequency (Fig. 6C). These effects were present with the gap junctions added to the baseline network containing basket cells (dashed lines, 6B-C), and were even more prominent when the basket cells were removed. For low coupling (0.001 μS, no basket cells), coherence was not as high as the basket cell case, though the oscillation frequency was much higher. Similar results were found for 0.005 μS coupling (not shown). For higher coupling levels (0.01, 0.05 μS, no basket cells), coherence was much higher than with basket cells alone (6B), as was the oscillation frequency (6C). In fact, for all values of gap junction conductance, the oscillation frequency was identical for a given level of noise, and was also identical to a single cell at the same noise level. These results show that, through the effects of CR, gap junctions can produce fast coherent oscillations in the ripple range, but require extensive connectivity and/or loss of basket cells to be effective.

Coherent oscillations with recurrent connections

The last method of coupling simulated was recurrent synaptic connections. These connections are quite common in the hippocampal CA3 region—over 25% of connections can be
recurrent axons (Wittner, Henze et al. 2007)—but much less so in CA1 (around 1/130 cells are
connected with recurrent axons (Bernard and Wheal 1994)). Two levels of recurrent connections
were simulated. In the first, a total of 4 pyramidal cells (5% of cells) were connected via AMPA
synapses to the A1 dendrites of 3-6 other pyramidal cells, for a total of 18 synapses. With basket
cells present, there was no appreciable difference in output (data not shown). As with the sparse
gap junctions, the oscillations produced by the basket cells were more powerful than any effect
of the recurrent connections. A more extreme case of recurrent connections was then
implemented, consisting of 10 pyramidal cells each connected to 8 others via recurrent
connections, for a total of 80 connections distributed over 50 cells. This represented significant
axonal sprouting, and is shown in Fig. 7. There was strong coupling between the connected
cells, but the network response did not oscillate very well, and was generally worse than if there
were no recurrent connections. Similar results have been found previously (Traub, Bibbig et al.
2000). The network contained a population of cells oscillating due to the basket cell coupling
described in Fig. 5, and a separate population oscillating at a faster frequency due to the recurrent
feedback. The two populations were asynchronous, so the output had lower coherence. When
basket cells were removed, the recurrent connections were able to produce coherent oscillations
at high frequency (> 120 Hz). This effect occurred at almost all noise levels, but there was
significant frequency jitter so the coherence was low at many points (7B). The oscillation
frequency was much faster with the recurrent connections even at low levels of noise, even faster
than a single cell’s response to the same noise level (7C). Although the response was different
from the predictions of CR, recurrent connections produced oscillations in response to noise that
were in the ripple range. When basket cell coupling was removed, the network output was a
coherent ripple-frequency oscillation.
Effects of adding noise to basket cells

Several simulations were then performed in which the basket cells received noise inputs as well as the pyramidal cells. In these simulations, the noise intensity for basket cells and pyramidal cells were independent. Thus, for each given basket cell noise intensity, a full range of pyramidal cell noise was simulated. The results, shown in Fig. 8, show several important effects. As noise caused basket cells to fire more frequently, they suppressed the pyramidal cells and made them less prone to fire in response to their own noise sources. This lowered the coherence (Eq. 2) of the network because the pyramidal cells fired more sparsely, and coherence was designed to measure only the pyramidal cell output. The result was a loss of the resonant coherence peak near $0.06 \text{ nA}^2$ (Fig. 8C, compare with Fig. 5B). The coherence was high when pyramidal noise was above $0.25 \text{ nA}^2$ regardless of basket noise intensity. The frequency of coherent firing, however, was strongly dependent upon basket cell noise, dropping almost linearly as basket noise increased (Fig. 8D). There were some minor irregularities when pyramidal cell noise was low and basket cell noise was high—the pyramidal cells were very suppressed and the network output was not a coherent oscillation, so measuring the peak frequency was somewhat unreliable (e.g. the non-oscillating pyramidal cell output in Fig. 8B, which generates very low coherence in 8C). Overall, increased basket cell activity due to noise reduced the frequency of pyramidal cell oscillations proportionally, and decreased the pyramidal cell coherence when pyramidal cells had low to medium noise levels.

Another important effect of basket cell noise is that, when the basket cells were coupled with gap junctions, they formed their own coherent oscillations. The basket cell oscillations had two key differences from those in pyramidal cells: they were not modulated by any inhibitory feedback, and they were faster. As seen in Fig. 8B, when connected by gap junctions, the basket
cells formed coherent 200 Hz oscillations in response to noise. There were only minor changes in the pyramidal cell output, similar to the earlier section with gap junctions between basket cells that did not have noise inputs. Although the pyramidal cell coherence did not change appreciably, the output of the basket cells was a coherent 200 Hz oscillation (composed of GABA inhibitory postsynaptic currents (IPSCs)) that produced sparse firing in pyramidal cells. When the pyramidal cells received no noise, the basket cells still produced coherent ~200 Hz oscillations, but the pyramidal cells never fired any action potentials (not shown). This simulation therefore demonstrates that increased synaptic noise and gap junctions in the basket cells produce characteristics similar to a sharp-wave associated physiological ripple (Ylinen, Bragin et al. 1995): 200 Hz IPSC output with sparse or absent firing of pyramidal cells. Later work will explore the relationship between these findings and experimental recordings of typical ripple oscillations.

DISCUSSION

On the physiological relevance of model parameters

While the basic model used in this study has been presented and validated previously (Tort, Rotstein et al. 2007), the current configuration contains new noise inputs and coupling that need to be justified physiologically.

Noise inputs

The neurons in this model received noise inputs in the form of random excitatory synaptic events. This is in contrast to the original configuration of the model, in which DC current was used to generate oscillatory activity (Tort, Rotstein et al. 2007). A key finding of this work is that periodic oscillations can also be generated with synaptic inputs, which are the
primary physiological input to these cells. For the basis of the analyses used herein, any synaptic input that is independent of the signal of interest can be considered noise. Thus, even “normal” synaptic events are included as noise. This not only facilitates quantifying the response of the network through SR or CR, but also allows for analysis of each cell in terms of the sum of all its inputs (Rudolph and Destexhe 2004). Hence, these simulated neurons can be compared with physiological recordings in terms of the variance and DC shift generated by all inputs.

Recordings of quiescent CA1 pyramidal cells in slices have somatic voltage variance of 0.01 to 0.04 mV² (Wahl, Jack et al. 1997). Those figures were obtained under conditions that are vastly different than those seen by these cells in vivo. As described previously (Stacey and Durand 2001; Stacey and Durand 2002), there are numerous input sources that can change this level significantly. In particular, there are obviously input levels high enough to produce action potentials, which in this model corresponded to the threshold of 149 mV². Beyond that level, another form of quantification is needed, since it becomes difficult to interpret variance with frequent action potentials. The rate of action potentials and mean depolarization are more appropriate measures. In vivo recordings of neocortex in awake animals demonstrate a high conductance state, characterized by a highly variable depolarization of up to 20 mV (Destexhe, Rudolph et al. 2003). This state is due to a large amount of inputs into the cells, the majority of which are likely synaptic. During this period cortical neurons have lower input resistance and action potential discharges of up to 40 Hz. Recent work has also shown that pyramidal neurons function more like oscillators in vivo, when all synaptic inputs are present (Prescott, Ratte et al. 2008), and that signal detection is improved when the cells are in the depolarized state (Wolfart, Debay et al. 2005). Those physiological data were not obtained during seizures, but rather
represent a normal, active behavioral state. Obviously, the inputs during a seizure can be significantly higher.

Much of the data presented herein lie within the parameters recorded *in vivo* during these activated states. In our computer model, with baseline physiological parameters, basket cells present, and no gap junctions, output similar to the physiological high conductance state (16 mV depolarization, oscillations around 40 Hz) occurred with noise intensity about 0.1 nA^2 (second moment about zero, or variance plus the square of the mean). The depolarization with high noise levels increased asymptotically—a single cell had a 13 mV depolarization with 0.01 nA^2 noise (Supplemental Fig. 1B), while increasing the noise to 0.1 nA^2 produced about 16 mV depolarization (not shown). However, the firing rates for those two noise levels were very different: a single cell had Poisson firing with 0.01 nA^2 and oscillated at about 80 Hz with 0.1 nA^2 (Suppl. Fig. 1C). The response was similar in the full network, except that the oscillations were coherent and slower (~40 Hz) with 0.1 nA^2 noise (Fig. 5). Most simulations increased the noise further to a maximum of 0.33 nA^2. At that maximal level, the network cells fired at about 110 Hz and were depolarized about 18 mV. Therefore, by increasing the noise intensity by less than four times above the physiological high conductance state, the network produced oscillations similar to fast gamma or ripples. This increase in noise level is easily reconciled in epilepsy. There is already evidence from human EEG recordings that high frequency power (and thus variance) increases prior to seizures (Worrell, Parish et al. 2004; Worrell, Gardner et al. 2008). Previous work in hippocampal slices and computer models has demonstrated similar findings, that synaptic events occur prior to epileptiform activity (Chamberlin, Traub et al. 1990; Traub and Dingledine 1990). It is not unreasonable to assume that synaptic noise before or during a seizure could reach four times its normal baseline. Physiological ripples also occur
under non-epileptic conditions, but rely upon the synaptic barrage of large sharp wave inputs to
trigger them (Ylinen, Bragin et al. 1995), which also increases the synaptic activity for a brief
period.

Recurrent synaptic connections

Coupling in this network took the form of recurrent synaptic connections, gap junctions,
and basket cell inhibition. Recurrent axons are uncommon in CA1 (Bernard and Wheal 1994),
but in CA3 are more common, can play a prominent role in neural firing (Li, Somogyi et al.
1994; Jones, Stubblefield et al. 2007; Wittner, Henze et al. 2007), and can be increased in
epilepsy (Siddiqui and Joseph 2005). In epilepsy, there is evidence of increased synaptic inputs
to CA1 from the entorhinal cortex (Shetty 2002). Under baseline conditions, with no recurrent
connections, our model was similar to the CA1 region. We simulated two levels of recurrent
synaptic connections, one with 5% of neurons connected, and another with 50/80 cells
connected. The 5% case is a conservative estimate to simulate the effects of a process similar to
axonal sprouting in CA1, but would not be pathological in CA3. The latter case simulates a very
large number of recurrent axons, applicable to pathological sprouting in either CA1 or CA3.

Gap junctions

The study of gap junctions is an emerging field. They have been difficult to classify and
quantify, but they clearly play a role in signal detection. Gap junctions between interneurons are
known to play a major role in HFO generation (Simon, Olah et al. 2005; Fukuda, Kosaka et al.
2006; Saraga, Ng et al. 2006). Additionally, axo-axonic gap junctions between pyramidal cells
were predicted in computer simulations of HFOs (Traub, Schmitz et al. 1999), and in vitro and
microscopic work has shown evidence to corroborate this (Draguhn, Traub et al. 1998; Hamzei-
Sichani, Kamasawa et al. 2007). These two forms of gap junctions are well-known hypotheses
for oscillatory behavior in the hippocampus (Traub, Pais et al. 2003). The current model did not include axo-axonic gap junctions. The effect of interneuron gap junctions was not noticeable in the current CR analysis due to the connectivity and coherence measurement of this network—the basket cells were already strongly coupled due to the synaptic connections, and the coherence output did not monitor basket cells directly. This does not imply that basket cell gap junctions are not important, rather that the tuning of this computer model had already produced the synchronizing effect of the basket cell syncytium that is generated by gap junctions in vitro/in vivo (Amitai, Gibson et al. 2002).

The gap junctions that produced ripple frequencies in these simulations were dendro-dendritic connections between pyramidal cells. This form of gap junction has not been widely studied in hippocampal HFOs. Gap junctions between principle neurons are well known in other areas of the CNS: they are found in areas such as olfactory neurons (Migliore, Hines et al. 2005), spindle bursts in the barrel cortex (Minlebaev, Ben-Ari et al. 2007), oculopalatal tremor (Hong, Leigh et al. 2008), and have been tested with combined computer simulation/in vitro preparations (Tseng, Tsai et al. 2008). Dye injection studies in hippocampal CA1 pyramidal demonstrate 1.6 neurons coupled per injection with normal pH and 3.25 at 7.9 pH when bursting activity arises—indicating that a high level of gap junction connectivity is associated with synchronized bursting activity (Church and Baimbridge 1991). Within epilepsy research, there is much evidence suggesting gap junction formation or dysfunction play important roles in seizure formation (Talhouk, Zeinieh et al. 2008; Thompson, Jackson et al. 2008; He, Hsiang et al. 2009). There are, however, no standard quantitative parameters to describe the range of gap junction connectivity in vivo, in either normal or pathological conditions. To address this, our simulations used a broad range of gap junction coupling. In one extreme (0.001 μS), there was
negligible voltage change in the targeted cell, yet clear differences in signal output. At the other extreme, the conductance was high enough (0.05 μS) that most action potentials were likely to be duplicated in the coupled cell. Physiological systems likely lie between these extremes, though the precise parameters depend upon cellular structure and dynamics. Previous modeling work used similar parameters as those used herein: 25 nS – 1 μS for dendro-dendritic connections (Tseng, Tsai et al. 2008) or ~ 2 nS for axo-axonal connections (Traub, Schmitz et al. 1999).

Comparison with ephaptic interactions

The implementation of gap junctions in the model (current injection through a resistor) is also quite similar to the effects that would be seen with ephaptic interactions (Fox, Bikson et al. 2004). The main difference is that the input resistance lowers when a gap junction is inserted, whereas an ephaptic effect produces a simple direct current injection. However, conditions that produce increased ephaptic interactions, such as cellular swelling, also lower the input resistance (Fox, Bikson et al. 2004). Therefore, although ephaptic interactions were not specifically included in this model, they are likely to be quite similar to the results for these dendro-dendritic gap junctions. The primary difference would be connection with more neighboring cells than in the gap junction case.

Basket cells

The role of inhibitory interneurons is difficult to quantify, but is an inherent and critical part of computer models of brain activity (Traub and Bibbig 2000; Cunningham, Whittington et al. 2004; Tiesinga, Fellous et al. 2004; Netoff, Banks et al. 2005; Traub, Contreras et al. 2005a; Dyhrfjeld-Johnsen, Santhakumar et al. 2007; Tort, Rotstein et al. 2007). The parameters for the basket cells were identical to those used and justified previously (Tort, Rotstein et al. 2007), and
the conductance of the GABA synapse onto pyramidal cells (0-0.775 nS) is comparable to previous simulations (Traub, Bibbig et al. 2000).

Basket cells and noise improve signal detection

The ability of noise to improve detection of a subthreshold signal, or SR, has been described previously in neural models (Chiu and Bardakjian 2004; Kawaguchi, Mino et al. 2008), with excitatory and inhibitory noise sources (Rudolph and Destexhe 2003), *in vitro* hippocampal slices (Gluckman, Netoff et al. 1996; Stacey and Durand 2001), and a visual-stimulus *in vivo* study (Funke, Kerscher et al. 2007). To our knowledge, this is the first rigorous demonstration of SR in a physiological model of neocortex or hippocampus that includes inhibitory interneurons. A possible concern about the inclusion of inhibitory basket cells is that they could diminish the SR effect. However, the results show quite the opposite: for low noise levels the SNR was improved when the basket cells were present, both in a single cell and in the network. The inhibitory feedback occurs after a spike, which allows lone events to occur but inhibits secondary events that follow. The overall effect was a reduction in the background noise over a wide range of noise, similar to that seen in prior work with inhibitory noise sources (Rudolph and Destexhe 2003). At higher noise levels, the basket cells promoted synchronized periodic firing, which disrupted signal detection and diverged from the SR curve. These two effects are important factors in evaluating cortical networks for SR, as they likely play a role in any experimental preparation that contains inhibitory interneurons.

Similarly, improved coherent oscillations with basket cells is a rather novel method of coupling within CR literature, but well described in neurophysiology, such as with PING. In CR literature, the coupling is normally excitatory (Wang, Chik et al. 2000; Chiu and Bardakjian 2004; Balenzuela and Garcia-Ojalvo 2005), which is typically represented as gap junctions,
ephaptic connections, or excitatory synaptic connections in physiological computational models (Stacey and Durand 2002). This work demonstrates that CR is also present in this physiological case of basket cell inhibition.

Noise oscillations and epileptiform activity

The network model was able to generate periodic oscillations in response to random synaptic activity. These oscillations have many similarities, both in character and etiology, with epileptiform HFOs. Of particular interest was the finding that an increase in either intrapyramidal gap junctions (Draguhn, Traub et al. 1998) or recurrent axons (Jefferys and Traub 1998) could increase the frequency of the oscillations to the ripple range (100-190 Hz), especially when fewer basket cells were present. This configuration is very similar to the pathologic changes seen in epileptic tissue, and suggests a method by which pathologic ripples could be generated within such tissue. HFOs in these ranges are often correlated with seizures (Fisher, Webber et al. 1992; Dudek 2003; Bragin, Wilson et al. 2004; Worrell, Parish et al. 2004; Jirsch, Urrestarazu et al. 2006; Rampp and Stefan 2006). Ripples are often considered abnormal in hippocampal tissue (Bragin, Engel et al. 1999; Bragin, Wilson et al. 2004), though the characteristics that separate them from physiological ripples (Ylinen, Bragin et al. 1995) are still unknown (Engel, Wilson et al. 2003). In addition, these results produce the HFOs with pyramidal cell action potentials, which has been hypothesized as a way of identifying epileptiform ripples (Engel, Bragin et al. 2009). These results were similar to recent work demonstrating that pyramidal cells fire during the ripple peaks, with interneurons firing just afterward once the ripple begins (Le Van Quyen, Bragin et al. 2008). There were two important limitations of this model. First, at high frequencies the pyramidal cells in this model fire very fast, and experimental work to date shows sparse pyramidal cell firing in ripples (Csicsvari, Hirase et al. 1999a; Csicsvari, Hirase et al. 2009).
Second, this network was not able to produce oscillations in the fast ripple (≈250 Hz) range. Further work will evaluate the pathologic changes necessary to produce such frequencies.

The coherent noise oscillations described herein are a form of CR, which is typically described in other physical systems or in neural models that have more abstract physiological correlation (Wang, Chik et al. 2000; Chiu and Bardakjian 2004; Balenzuela and Garcia-Ojalvo 2005). Though the current model is an arbitrary and reduced structure, it is founded upon physiologic channel dynamics and synapse functions, and the input and output characteristics can be compared with true physiology. The oscillations were present under many different configurations and parameters, and appeared to be an inherent characteristic of the network.

When presented with enough input, any neuron is capable of repetitive firing. In a network, some form of coupling is required to synchronize constituent cells, and in this case the basket cells provided ample coupling. In our model, the firing frequency was determined by the interaction of the input, the refractory period of the cell, the rate of firing and synaptic characteristics of basket cells, and other complex network and channel dynamics. This hippocampal network had a propensity to fire from 40-100 Hz, the gamma range, when the background was highly active. These results were similar to the generation of gamma oscillations in Traub’s model (Traub, Jefferys et al. 1997). The model also reproduces the effect of NMDA blockade increasing gamma power, which is a model of schizophrenia (Pinault 2008; Lazarewicz, Ehrlichman et al. 2009). Our model predicts that this effect may be due to modulation of the interneuron activity, effectively altering the network frequency through the PING effect.

There are various theories about the generation of fast neural oscillations, and at times they appear to be mutually exclusive. For example, normal gamma oscillations and
physiological ripples appear to be produced by similar mechanisms: IPSP oscillations with sparse pyramidal cell firing (Ylinen, Bragin et al. 1995; Chrobak and Buzsaki 1996; Traub, Whittington et al. 1996a; Bragin, Engel et al. 1999; Tort, Rotstein et al. 2007). But others have shown HFOs that are formed by bursts of pyramidal cell population spikes (Bragin, Wilson et al. 2007) and can occur when IPSPs are blocked by bicuculline (Behrens, van den Boom et al. 2007). In addition, HFOs are described to be dependent upon either axo-axonic gap junctions (Traub, Bibbig et al. 2000), ephaptic connections (Fox, Bikson et al. 2004), or recurrent excitatory axons (Dzhala and Staley 2004). Reconciling these different conditions is difficult, but may provide insight into the pathology of epilepsy, particularly if one assumes there are two populations of HFOs—normal and pathological (Engel, Bragin et al. 2009). This manuscript describes a method that may link the two forms of HFOs: CR predicts and describes that various levels of noise and coupling can produce oscillations similar to both “normal” and “abnormal” oscillations. Under normal conditions, physiological levels of noise can generate network gamma oscillations through the PING mechanism as well as 200 Hz oscillations in the basket cells similar to physiological IPSP ripples. When noise and/or coupling are abnormally high, the network generates fast oscillations (fast gamma and population-spike ripples) in the pyramidal cells that are similar to epileptiform activity, even when basket cells are removed. The effects demonstrated in this paper occurred with inputs that are very plausible physiologically, and were not dependent on any specific or ordered coupling configurations. This work suggests that noise oscillations are an inherent property of hippocampal networks. In addition, this network is only subtly different from neocortex, and these same principles also are likely to apply to neocortical oscillations.
CONCLUSION

This work demonstrates how synaptic noise and coupling can improve signal detection and generate coherent oscillations in a hippocampal computer network. The parameters that generated these effects are physiologically feasible. We propose that SR and CR are tools that can quantify inherent properties of neural systems when noise and coupling are favorable, and that both the high conductance state (Destexhe, Rudolph et al. 2003) and seizures provide such conditions. Noise clearly plays an important role in signal processing, and may be an important factor in the generation of epileptiform oscillations.

There is tremendous clinical activity involved in treating people with epilepsy, but there are fundamental gaps in our understanding that hinder this mission. Several such gaps are our lack of understanding of what distinguishes epileptic networks from normal brain, what constitutes a seizure, and what generates individual epileptic events, both “pathological” interictal oscillations and ictal phenomena. More specific questions arise from recent work identifying HFOs, especially ripples and fast ripples, as potential markers for epileptogenic regions. The mechanisms generating these events are still unclear. Computer simulations, provided they are grounded on physiological constraints, provide powerful tools for exploring the mechanisms of such phenomena that are currently beyond electrophysiologic technology. Our study suggests that synaptic activity quantified as “noise” and network coupling generate both normal and abnormal coherent oscillations. Furthermore, it predicts that changes in the noise and/or the coupling similar to those seen in epilepsy can generate pathological HFOs. As technology becomes able to monitor and modulate noise and coupling in physiological networks, these principles can be explored in vitro and in vivo on the network scale.
Acknowledgements:

This research was supported by the Epilepsy Foundation Merritt-Putnam fellowship, through the generous support of Pfizer, Inc.; by the National Institutes of Health (2RO1NS041811-07); and the University of Pennsylvania Institute for Translational Medicine and Therapeutics.

Special thanks to M. Dichter and D. Contreras for their helpful comments. We also express gratitude to the late Leif Finkel, who inspired this project.


Figure 1 Schematic of model. A: Single pyramidal cell with soma, basal dendrite, 3-segment apical dendrite, and synaptic input to introduce "noise." Output is pyramidal somatic membrane voltage. B: Basket cell receives AMPA synapse (solid line) from pyramidal cell, and sends GABA synapse (dotted) back to the pyramidal cell apical dendrite. The basket cell afferent synapse from pyramidal cells contained NMDA current in addition to the AMPA in one simulation. In a separate simulation, the basket cell received an additional, independent AMPA noise synapse. C: Network connections, each cell represents 20. Output of network is the averaged somatic membrane voltage of all 80 pyramidal cells. Each pyramidal cell has an independent noise synapse. Each basket cell (20) synapses with all 80 pyramidal cells.

Figure 2 SR in a single neuron. A: Raw voltage data from a single cell with varying amounts of noise, with and without a subthreshold 16 Hz signal. Shaded lines are added to visualize alignment, and are aligned with data in C. All data are 1 s long. B: Power spectral density (PSD) of data in lines 2-4 of A. By definition, the PSD is zero with noise = 0 nA^2, as there is no output (action potentials) from the cell. SNR is calculated as the ratio of PSD power at 16 Hz and the average baseline power around that point. Note that for the second line the SNR is < 1 because the signal power is less than the nearby baseline. (Box, diamond: correspond to data points in D). Bottom two PSD plots show the response to noise alone without the 16 Hz signal for comparative purposes. C: A basket cell is added as in Fig 1B. Synaptic strength is that of 20 basket cells. Raw data show reduction in noise (compare with line 3 in A). Dashed line below the voltage tracing indicates signal frequency for both A and C. Bottom: PSD of these data, generating the circle indicated in D. D: Plot of SNR versus noise intensity with and without basket cells. Sample data from B and C are indicated by their corresponding shapes. In general, SNR > 10 corresponded good signal detection. Without basket cells the SNR is much lower due to increased random firing. For comparison, a sample SR curve generated from Eq. 1 is included (fits only the first two data points for "20 baskets"). It does not fit the data well for high levels of noise (see text).

Figure 3 SR in hippocampal network. A: Raw output of network when 20 pyramidal cells received subthreshold signal plus noise at 3 different intensities. Spike raster plots (top) show response of basket cells (top 20 cells) and pyramidal cells (bottom 80 cells). Network output (bottom) is the average membrane voltage of all pyramidal cells. Five groups of 4 pyramidal cells receive the subthreshold signal (duration 1 sec). Left: only the 20 signaled cells fire with 0.0014 nA^2 noise. Middle: at 0.03 nA^2, the network oscillates at twice the input frequency (32 Hz). The 16 Hz signal is still present. Right: At high noise, the network oscillates at faster frequencies, ignoring the input signal. B: PSD for the three noise levels, with calculated SNR as shown. Arrows indicate signal frequency of 16 Hz. C: SNR plot for the network. Oscillations produced at noise levels above 0.01 nA^2 corrupt detection of the input signal, leading to unusual SR curve fit (see same curve in different scale in 4B). Boxes: data for three examples in A.

Figure 4 Network effects in SR.
A: Raw voltage of network with and without basket cells for 0.01 nA² noise. With baskets (left, same series as in Fig. 3), the nonsignaled cells fire at 16 Hz but antiphase with the signal. Without baskets, noise is much more prominent and SNR is lower. Arrows indicate the 16 Hz signal. B: SNR of the network with and without basket cells, and additionally when only a single cell received the 16 Hz signal. SNR for 4 signaled cells was between the data for 1 and 20 (not shown). Detection of the subthreshold signal is greatly improved by the presence of basket cells and more signaled cells. C: Peak frequency of the oscillations in the network with and without the 16 Hz input signal. For noise < 0.15 nA², the signal input entrains the network to its harmonics even if the SNR is low.

Figure 5 Coherence resonance.

A: Response of the network to three levels of noise, without any periodic signal input. Power spectrum for each (bottom) shows peak power at 20, 36, and 69 Hz, respectively. Data are for the baseline basket conductance of 0.275 nS. The coherence for 0.06 nA² noise was much greater than the other two. Illustrations of h and Δω are indicated by dashed and dotted lines on each PSD plot, and produce the indicated coherence β. B: Coherence as a function of noise and basket cell conductance. Data in A are marked with circles. Increasing coupling raised the coherence. Increasing noise improved coherence at lower levels, then degraded it. For very high noise, coherence returned to high levels. Note lack of resonant peak without any basket cells (far right). C: Frequency response of the network. Increased coupling lowered peak frequency; noise increased the frequency.

Figure 6 Coherent oscillations with gap junctions

A: Left: with 39 gaps scattered randomly, there are clusters of neurons firing together near bottom of raster, but the overall network coherence is less than without gaps (see Fig. 5). Middle: in the extreme case of having all neurons connected together by 79 inline gaps, the cells all fire together, but coherence is not very high due to frequency jitter. Right: without basket cells, the inline network coherence is very high. All plots 1 s long.

B: With inline gaps and baskets removed, coherence for three levels of coupling strength are all greater than that produced by basket coupling alone as in Fig. 5. Addition of the basket cells to the inline gaps (dashed line, "+B") also reduces coherence. Box: data indicates in A and Fig. 5 C: Frequency response of network with inline gaps and no basket cells is identical to that of a single cell, even at very low conductance, and is in the ripple range. Addition of basket cells lowers frequency to gamma range (dashed line). Frequency was faster in all cases than for the basket cell coupling alone.

Figure 7 Recurrent axons generate fast oscillations.

A: Raw voltage and PSD for network with 80 recurrent axons with ("+B") and without ("-B") basket cells. Bottom: The network oscillated much faster without basket cells (70 vs. 176 Hz). All data shown are for 0.15 nA² noise. B: Coherence for the network with recurrent axons is generally lower than the data in Fig. 5 (in which basket cells are the only coupling mechanism). C: Frequency response of data in A, compared with that of a single cell and the data in Fig. 5. Basket cells maintained the network output in the gamma range, despite the recurrent axons. When basket cells were removed, the network oscillated faster than even a single neuron, and well into the ripple range. Figure legend in C applies also to B.

Figure 8 Effect of noise added to basket cells
A. Spike raster plot for network in which basket cells receive 0.03 nA^2 noise intensity, and pyramidal cells receive 0.08 nA^2. Baskets fire much faster, and pyramidal cells more suppressed, than in other figures without basket cell noise (note A and B here are 300 ms long, while similar plots in other figures are 1000 ms). Blue trace on bottom is the summed pyramidal voltage output, red trace is the summed basket output (spike histogram). B. Same parameters as in A, except basket cells are connected with strong gap junctions. Baskets tend to fire coherently at about 200 Hz. Pyramidal cells fire sparsely but do not form coherent oscillations. With lower noise to the pyramidal cells, they stop firing completely, but basket cells continue to fire at ~200 Hz (not shown). C. Coherence of the network (pyramidal cell output) for different basket cell noise intensities. Included is the response for 0 nA^2 basket noise (far right), which is identical to Fig. 5. With added basket cell noise, the resonant peak at low noise disappears, but the coherence is still very high for high noise levels. Legend on bottom is for both C and D. D. Frequency response of data in C. Increasing basket noise for a given pyramidal cell noise intensity lowers the oscillation frequency almost linearly. The irregularities for high basket noise/low pyramidal cell noise are due to strong suppression of the pyramidal cells (see text).

Supplemental Figure 1 Oscillations in a single cell due to random noise
A. Raw voltage data for three levels of noise intensity in a single pyramidal cell. Poisson firing at low noise transitions into periodic oscillations. Bars represent 200 mV and 200 ms. B. Mean depolarization of a single cell for increasing noise. C. Oscillation frequency for increasing noise with three levels of basket cell inhibition. The basket cells lower the firing rate.

Supplemental Figure 2 Effect of NMDA current on CR.
A: Three dimensional plot of power spectra for the network response with varying levels of NMDA current on the afferent pyramidal-to-basket cell synapses. The NMDA current is defined as a specified ratio of the AMPA current. All other parameters were unchanged from the baseline in Fig. 5. The pyramidal cell noise was 0.06 nA^2. Gamma frequency power decreases as more NMDA current is introduced. B: Three dimensional plot of power spectral data with 0.22 nA^2 noise. There is significant change in both the peak oscillation frequency and the total gamma power as NMDA current increases. C: Coherence for various levels of NMDA current. There were no oscillations for ratios of 0.1 and 0.5. The coherence for 0.1 was actually slightly higher for low noise levels. D: Plot of peak oscillation frequency versus noise intensity, for varying levels of NMDA current. The difference is most pronounced for high noise levels. The response of the 0.1 ratio is irregular because it is not oscillating, and the "peak frequency" is somewhat random due to low coherence. E: Plot of total gamma power as a function of NMDA current for two noise levels. Gamma power was computed by integrating the power spectrum from 30-100 Hz. For both low (0.06 nA^2) and high (0.22 nA^2) noise, the total power decreased as NMDA current increased, reaching nearly 0 for a ratio of 0.1.
Output = V_m

AMPA “Noise” synapse

Basket cell

AMPA Synapse (+ optional NMDA)

GABA synapse

AMPA “noise” (basket)

Output = average of all V_m

AMPA Synapse

Output = V_m

AMPA Synapse (+ optional NMDA)

GABA synapse

AMPA “noise” (basket)
A

Signal + 0 nA²
Signal + 0.0014 nA²
Signal + 0.01 nA²
0.0014 nA² no signal
0.01 nA² no signal

100 mV
1 second

B

SNR = peak PSD/ baseline = 17.8
SNR = 0.4

PSD
(mV²/Hz, log scale)
0 50 100 150 200

Frequency (Hz)

C

Signal + 0.01 nA² + 20 baskets

SNR = 11.4

D

SNR
0 1 10 100
0 0.01 0.02 0.03

Noise Intensity (nA²)

Frequency (Hz)

no baskets
20 baskets
SR

log scale
A

0.0014 nA^2

0.03 nA^2

0.06 nA^2

Baskets (raster)

Pyramidal (raster)

Raw voltage 20 mV

1 second

B

SNR = 132

SNR = 0.9

SNR = 0.02

PSD mV^2/Hz

0 Hz 100 200 Hz

C

SNR

Network SNR

SR equation

Noise Intensity (nA^2)
**A**

0.01 nA² with baskets  
0.01 nA² without baskets

Spike raster  
Raw voltage 20 mV  
PSD

**B**

- Green triangle: Signal to 20 cells, no baskets
- Purple square: Signal to 1 cell
- Blue triangle: Signal to 20 cells (Fig. 3C)
- Blue line: SR equation (Fig. 3C)

SNR

Noise Intensity (nA²)

**C**

- Blue diamond: Noise alone
- Red square: Noise + signal

Peak Frequency (Hz)

Noise intensity (nA²)
A

Noise only:
0.008 nA²

0.0826

0.186

0.309

Basket cell conductance

Intensity

Oscillation Frequency (Hz)

Basket

Pyramidal

20 mV

PSD

B

C

Basket cell conductance

Noise Intensity (nA²)

Oscillation Frequency (Hz)

Basket cell conductance

Noise Intensity (nA²)
A

Recurrent axons with baskets, 0.15 nA²

Recurrents without baskets

Voltage

20 mV

500 ms

PSD

B

C

Fig. 5

Single cell
Recurrnts (+B)
Recurrnts (-B)

Coherence

Oscillation Frequency (Hz)

Ripples
Fast gamma

0 0.1 0.2 0.3

Noise Intensity (nA²)

0 100 200

Noise Intensity (nA²)
**A**

Basket noise 0.03 nA²; Pyramidal noise 0.08 nA²

No gap junctions

Strong basket gap junctions (1e-4 μS)

**B**

200 Hz IPSP oscillations, with sparse pyramidal cell firing: typical of ripples

**C**

200 Hz IPSP oscillations, with sparse pyramidal cell firing: typical of ripples

**D**

Pyramidal noise (nA²)

Basket noise (nA²)
A

B

C

Depolarization (mV)

Noise intensity (nA²)

Oscillation frequency (Hz)

Noise intensity (nA²)
A

Power Spectra (mV^2/Hz)

0 Hz          100 Hz          200 Hz

B

Power Spectra (mV^2/Hz)

0 Hz          100 Hz          200 Hz

C

Coherence

0.01          0.05          0.1

D

Ratio of NMDA/AMPA

0.01          0.05          0.1

E

Ratio of NMDA/AMPA

0.01          0.05          0.1