Published in final edited form as:

Neurocomputing. 2007 June ; 70(10-12): 2074–2078. doi:10.1016/j.neucom.2006.10.086.

Theta-Modulated Input Reduces Intrinsic Gamma Oscillations in a Hippocampal Model

Ashlie B. Hocking^{a,b} and William B Levy^{a,1}

^a Department of Neurosurgery, University of Virginia, Charlottesville, VA

^b Department of Computer Science, University of Virginia, Charlottesville, VA

Abstract

Introducing theta-modulated input into a minimal model of the CA3 region of the hippocampus has significant effects on gamma oscillations. In the absence of theta-modulated input, the gamma oscillations are robust across a range of parameters. Introducing theta-modulated input weakens the gamma oscillations to a power more consistent with power spectra acquired from laboratory animals. With these changes, simulations of the hippocampal model are able to reproduce hippocampal power spectra measured in awake mice.

Keywords

Fourier transform; power spectrum; CA3 region; membrane potential; cognition

Introduction

Previously, we demonstrated a minimal model of the CA3 region of the hippocampus that produces gamma oscillations as an emergent behavior of the network [3]. The gamma oscillations were emergent in the sense that no identifiable oscillator operating at the gamma frequency exists, but the collective behavior of the neurons exhibited a gamma oscillation. Although the frequency of the gamma oscillations is robust to a wide range of model alterations, introducing theta-modulated input has a significant impact on the power of the gamma oscillations. The power spectrum generated by a fast-Fourier transform (FFT) is much more similar to power spectra recorded from experimental subjects [2].

This model can be compared to models by Mann et al. [8] and Kopell et al. [5] which have interneurons synchronizing the gamma oscillations. In contrast, although this model does use interneurons to approximately control activity, the interneurons have no time constant contributing to the frequency of the gamma oscillations.

Methods

The model extends the 1996 Levy minimal model [6] of CA3, by replacing the McCulloch-Pitts neurons with integrator-based excitatory spike-passing neurons incorporating

¹Corresponding author, E-mail address: E-mail: wbl@virginia.edu.

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Izhikevich's [4] modifications to the Fitzhugh-Nagumo equations, as described in Table 1. Additionally, trivial equations governing synaptic activation and somatic current injection were added to allow the model to be run at any time-scale without changing the results significantly.

The excitatory neurons have a sparse, asymmetric, recurrent connectivity to each other. That is, the connectivity matrix c_{ij} is randomly generated such that each neuron receives input from exactly 10% of the other neurons in the network and the output of one time-step is the input to the next. Feedback and feedforward inhibitions help to control network activity approximately, where network activity is defined as the fraction of neurons active in each time-step of the simulation.

In addition to being fired recurrently ($v_j(t) \geq v_{thresh}$), neurons also have the possibility of being fired externally (i.e., by neurons outside of the model, described by $x_j(t) = I$). A pattern in the simulation is defined by a range of neurons that each have a probability p_e of firing. These patterns are combined to create a circular sequence, on which the simulations are trained.

Theta-modulated input was presented using several different techniques. In all cases, the input was modulated by the changing the probability a neuron would be externally activated. The simplest technique involved using a sine wave such that the probability a neuron would be externally activated is

$$p_e = A + B \sin(\omega_\theta t), \quad (7)$$

where $\omega_\theta \approx 43.9$ Hz corresponding with a theta frequency of approximately 7 Hz. B was set to one-half of A such that the maximum probability of being externally activated was three times the minimum probability. To achieve some asymmetry in the theta oscillations, a second periodic function, shown in Fig. 1, was also used, although only for the last simulation (Fig. 5). This periodic function, $S(x)$, is given by

$$S(x) = \begin{cases} 0, & 5\pi/3 < x < 2\pi \\ -1 + x^{0.4} e^{\frac{x}{18}}, & 0 < x < 5\pi/3 \end{cases} \quad (8)$$

As with the sine wave, simulations using this periodic function would have neurons externally activated with a probability

$$p_e = A + BS(\omega_\theta t - \pi/3). \quad (9)$$

The frequency at which the input was modulated was fixed for some simulations and allowed to randomly vary (from cycle to cycle) in other simulations. The period of modulation would be 143 ms when fixed and between 133 and 153 ms when allowed to vary.

A fast Fourier transform is used to generate a power spectrum of the total network activity, $\sum_{i=1}^n z_i(t)$, with a brick wall filter due to the resolution, or time-step size, of the simulation. For example, when the time-step size is 0.5 ms, the brick wall filter is, as a result of this time-step size, approximately 2000 Hz. Results for the power spectrum are therefore only valid up to 1000 Hz. The result of the fast Fourier transform is multiplied by its complex conjugate and divided by the sample size to achieve the power spectrum across frequencies. The resulting

power spectrum is then collected into bins of width 1 Hz. Results above 100 Hz are omitted in order to emphasize the frequencies of interest.

Results

In the absence of any theta-modulation, gamma oscillations were quite strong and centered around 50 Hz. Figure 2a show the fast-Fourier transform of the net activity ($\sum_{i=1}^n z_i(t)$), and Fig. 2b shows the log of the FFT converted to dB, i.e., multiplied by 10.

When this same network is trained on theta-modulated external input and then allowed to run in the absence of any input, a very low power oscillation in the theta band is now visible (Fig. 3). Additionally, the central frequency of the gamma oscillation has shifted from 50 Hz to approximately 64 Hz, and the gamma frequency oscillation is more spread.

If instead, the network is driven at theta-modulated input, the gamma oscillations become much less powerful. Although not visible on a linear scale, Fig. 4a, the log of the FFT reveals that the gamma oscillations are still present, but are several orders of magnitude weaker than in the absence of theta-modulated input (Fig. 4b).

One problem with the theta-modulated input in the model is the non-biological strength of the first, second, and even third harmonics of theta. To address this issue, the frequency of the theta-modulated input is jittered from one cycle to the next. Specifically, for each presentation of the circular sequence, a new period of theta is calculated based using a truncated normal distribution whose mean is the period of the last circular sequence and whose standard deviation is 20% of that mean, truncated below 133 ms and above 153 ms. The introduction of jittered theta substantially reduces the power of the theta-associated harmonics relative to the non-jittered theta while keeping gamma oscillations subdued relative to the absence of theta (Fig. 5 & 6).

Discussion

These simulations show that adding theta oscillations to a simple CA3 model has a significant impact on gamma oscillations. Furthermore, adding variability to the frequency of these theta oscillations results in a power spectrum that resembles those recorded from the hippocampus in mice [1].

Here we only trained the simulations on a circular sequence, and all simulations demonstrated the ability to recall the training sequence when given only the initial pattern in the sequence. However, sequence learning has been shown to be an important antecedent in our model for the acquisition of other cognitive behaviors [7]. The addition of theta and the intrinsic generation of gamma in a model that reproduces these cognitive behaviors promises to lend insight into the roles that these oscillations have in learning and cognition. Furthermore, being able to reproduce realistic EEG-like recordings from simulations engaged in these cognitive tasks improves the ability to validate the model.

Being able to selectively strengthen and weaken gamma oscillations in a cognitive model of the hippocampus will allow further research into possible effects of hippocampal gamma oscillations on certain forms of cognition. Reproducing power spectra recorded from animals will provide an additional set of constraints to help reduce the increased degrees of freedom introduced by the addition of new biological parameters.

Acknowledgments

This work was supported by NIH MH63855 to WBL, the Meade Munster Foundation, and by the Department of Neurosurgery.

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Biographies

Ashlie B. Hocking earned a BS in Physics from Georgia Tech, an MS in Physics/Astronomy from Georgia State and a Masters in Computer Science from the University of Virginia and is currently pursuing his PhD in Computer Science from the University of Virginia. His research is performed under the guidance of William B Levy in the Laboratory of Systems Neurodynamics.

William B Levy earned a BA in Psychology from Princeton and a PhD in Psychobiology from the University of California Irvine. He was a Psychology professor at the University of California Riverside from 1974 until 1979 at which point he joined the faculty at the University of Virginia, where he is currently a professor in the Neurological Surgery department and in the Psychology department.

Figure 1. Periodic function used to modulate input. This periodic function (Eq. 8) is designed to crudely approximate the reaction of neurons in the presence of changing stimuli.

Figure 2.

Power spectrum of a simulation in the absence of any external input demonstrating emergent gamma oscillations. When the network is allowed to run without any input, a very sharp gamma oscillation is present, as is its harmonic. A low-powered oscillation is also visible at approximately 3–4 Hz, which is more noticeable in Fig. B. In both figures, the absolute power in the FFT is normalized to 1.

Figure 3.

Power spectrum in a simulation without external input after training on theta-modulated input. The FFT shown here is for the same network as in Fig. 2, but after training the network using theta-modulated input. In both figures, the absolute power in the FFT is normalized to 1.

Figure 4.

Power spectrum for simulations in the presence of a theta-modulated input. The log of the FFT reveals that gamma still exists but is more than 100 times weaker than in the absence of theta-modulated input. In both figures, the absolute power in the FFT is normalized to 1.

Figure 5.

Power spectrum for simulations with a theta-modulated input with a variable frequency reduces the power in the harmonics of theta. Theta oscillations are clearly visible at 7 Hz, as are sub-harmonic oscillations at approximately 3–4 Hz. Harmonic oscillations of theta are also visible at 14 Hz, and gamma oscillations are visible from 40 to 90 Hz. At this point, the power spectra are similar to those recorded in mice [1]. In both figures, the absolute power in the FFT is normalized to 1.

Figure 6.

Adding jittered theta-modulated input reduces the total power present in gamma. Comparing the power spectra for a simulation where theta is not present (dashed line) and for a simulation with a jittered theta (solid line), demonstrates the effect on the power of gamma oscillations due to theta-modulated external input. These power spectra are not normalized to demonstrate that the reduction in gamma is not an artifact of normalization.

Table 1

Equations of the Levy model using Izhikevich-based neurons. The following parameter settings were used: $a = 0.02$, $b = -0.1$, $c = -55$, $d = 6$, $e = 4.1$, $f = 108$, $v_{thresh} = 30$, $\mu = 0.05$, and $\tau_{on} = 15$ ms. The parameters for the Izhikevich equations (i.e., a , b , c , d , e , f , and v_{thresh}) were those from the Izhikevich integrator neuron [4], and the learning rate μ was chosen based on results[6] from previous studies. The parameter α was based on the size of the time-step used in the simulation – specifically, $\alpha = e^{-\Delta t/T}$, where T is the off-rate time constant of the NMDA-receptor, set to 143 ms. The constant, g , and the inhibition constants, K_{FB} , K_0 , and K_{FF} , were set in such a way to achieve a desired average firing rate of the neurons – usually 2 Hertz. The connectivity ratio, c , of the network is 10%, such that each neuron receives synaptic input from $c \cdot n$ neurons, where n is the number of neurons in the network (from 4,000 to 6,000 in the simulations here). The connectivity matrix, c_{ij} , is $\{0, 1\}$ valued where a 1 indicates that neuron i provides input into neuron j . Φ_i is the time at which neuron i last fired. $x_j(t)$ is 1 if a neuron is externally activated.

$$\text{Synaptic activation : } s_j(t) = \sum_{t=0}^{-1\text{ms}} z_j(t - \Delta t) \quad (1)$$

Dendritic excitation :

$$y_j(t) = \frac{\sum_{i=1}^n c_{ij} w_{ij}(t) s_i(t)}{\sum_{i=1}^n c_{ij} w_{ij}(t) s_i(t) + K_{FB} \sum_{i=1}^n z_i(t) + K_0 + K_{FF} \sum_{i=1}^n x_i(t)} \quad (2)$$

$$\text{Somatic current injection : } I_j(t) = \sum_{t=0}^{-10\text{ms}} y_j(t) \quad (3)$$

Somatic firing : (Izhikevich equations with external activation)

$$\begin{aligned} \frac{\partial v_j}{\partial t} &= 0.04 v_j^2(t) + e \cdot v_j(t) + f - u_j(t) + g \cdot I_j(t) \\ \frac{\partial u_j}{\partial t} &= a(b \cdot v_j(t) - u_j(t)) \\ \text{if } v_j(t) &\geq v_{thresh} \text{ or } x_j(t) = 1 \text{ then} \\ v_j(t) &= c, \quad u_j(t) = u_j(t) + d, \quad \text{and } z_j(t) = 1 \text{ (Neuron fires)} \\ \text{else} \\ z_j(t) &= 0 \text{ (Neuron does not fire)} \end{aligned} \quad (4)$$

Synaptic modification rule :

$$\Delta w_{ij}(t) = \mu z_j(t) [z_i(t - 1) - w_{ij}(t)] \quad (5)$$

Pre - synaptic time - averaging firing (with rise) :

$$z_i(t) = \begin{cases} t - \Psi_i / \tau_{on}, & \text{if } \Psi_i \leq \tau_{on}, \text{ and} \\ az_i(t - \Delta t), & \text{otherwise} \end{cases} \quad (6)$$