**Introduction**

**Abstract**

Hippocampal sharp wave ripples (SPW-R) are the most synchronous population pattern in the mammalian brain, and have been identified as key biomarkers for important brain functions such as memory consolidation, curiosity, and decision making [1]. These events occur between 110-250 Hz in humans.

Accurate mathematical models of SPW-Rs can provide both insight into their generation and their downstream effects. Physiologically-based mathematical models for the CA3 and CA1 regions of the hippocampus have been created that, when connected together in a feedforward manner, can accurately reproduce many of the basic characteristics of SPW-Rs [2]. These models are able to provide insight into the generative mechanisms underlying the SPW-R complex.

The goal of this project was to use a SPW-R mathematical model to investigate the effect that interneuron-interneuron connections in CA1 have on ripple generation, as this has not been explored in the literature that we reviewed. The major finding of this project was that for a constant 0.3 nA input current to a network of 1000 CA1 interneurons, the optimal probability to maximize power in the ripple frequency band (140-200 Hz) was 0.4.

**Background**

The hippocampus is essential for many types of memory, as well as general memory consolidation and recall [3]. The hippocampus is able to accomplish these functions in part due to its dense packing of neurons, which generate large LFPs and brain rhythms [1]. Brain rhythms are periodically fluctuating waves of neural activity. These rhythms are synchronous events caused by the activity of large populations of neurons. This synchrony allows the brain to perform complicated cognitive functions, such as memory, that are too complex to be computed by individual neurons. Brain rhythms are especially prominent in area CA1 of the hippocampus, in which the pyramidal cell dendrites are aligned in parallel. The pyramidal cell is the main excitatory neuron in the hippocampus. Activity across large populations of pyramidal cells is synchronized by hippocampal interneurons, which allows for the generation of brain rhythms [4]. Additionally, pyramidal cell activity is modulated by, and generates brain rhythms. Within the local field potential (LFP) of the hippocampus, there are three major types of brain rhythms: theta, sharp wave-ripples, and gamma. We will primarily be focusing on sharp wave-ripples for this project.

The sharp wave-ripple (SPW-R) complex consists of a 110-250 Hz ripple oscillation superimposed on a .01-3 Hz sharp wave [1]. Together, the sharp wave-ripple complex consists of fast (110-250 Hz) oscillatory events that occur during low frequency waves (<3 Hz) in humans [5]. SPW-Rs often occur during sleep and resting states, and largely arise in the hippocampus, although they have also been observed in the entorhinal cortex [6]. In the hippocampus, however, they are very widespread and extend throughout the CA3-CA1-subiculum complex-entorhinal cortex axon [7]. Sharp wave-ripples are important for consolidating and stabilizing memories [8]. Due to the strong transient output of the LFP during SPW-Rs, they likely have an effect on neocortical targets, and could be a mechanism for transfer of memories from the hippocampus to the neocortex for long-term storage [2]. SPW-Rs have also been proven to be critical to spatial navigation tasks, specifically for the excitation of place cells that allows them to fire outside of their place fields, and thus retrieve spatial memories of distant locations [9]. Additionally, sharp wave-ripples have been hypothesized to be important for intrinsically driven processes in the hippocampus, such as memory retrieval and imaginary events. Evidence for this is that during sharp wave-ripples, place cell sequences can represent paths not actually physically taken [10]. Despite their importance, however, the mechanism underlying the SPW-R complex is not well-understood.

One proposed mechanism for sharp wave-ripples is that sharp waves are triggered by a population burst of activity from CA3 pyramidal cells [11]. Sharp waves then propagate through the Schaffer collaterals from CA3 to CA1 and trigger a depolarization of CA1 pyramidal cells and interneurons [12]. This depolarization causes synchronous firing of CA1 interneurons at ripple frequencies (110-250 Hz). When a critical number of interneurons fire at ripple frequencies, they cause phase locking in their pyramidal cell targets at ripple band frequencies. Thus, synchrony is able to be established quickly through the interactions between pyramidal cells and interneurons. Another proposed mechanism is that axo-axonal gap junctions between CA1 pyramidal cells allow them to fire at ripple band frequencies [13]. Evidence for this mechanism is mixed, as ripples are suppressed under gap-junction blockers, but SPW-R generation does not happen when CA1 pyramidal axons are stimulated [14, 15].

**Hippocampal Model**

The mathematical model used in this project consists of the combination of two physiologically-realistic models of CA1 and CA3 [2]. The CA3 model primarily consists of long-range, recurrent excitatory connections and the CA1 model primarily of strong inhibitory connections. However, both models do consist of connections between inhibitory and excitatory populations. These models have been separately shown to successfully reproduce physiologically accurate properties of their respective hippocampal areas. The CA3 model exhibits population bursts that are periodic in the theta frequency band (4-10 Hz) and the CA1 model exhibits population oscillations at or above the gamma frequency band (40-100 Hz). To recreate a full hippocampal model, the CA3 model uses excitatory connections to feed forward into the CA1, mimicking Schaffer collaterals. This full CA3-CA1 network produces synchronized oscillatory events between 150-200 Hz in CA1 in response to excitatory input from CA3 population bursts. These closely resemble sharp wave-ripples and are shown to share defining characteristics with real SPW-Rs from neurophysiological recordings.

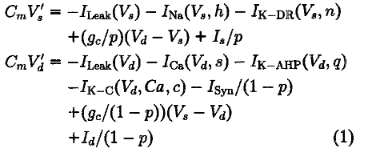
**Methods**

**Model Architecture**

In the hippocampal model that we used, the CA3 and CA1 submodels are one-dimensional arrays containing 1000 pyramidal cells and 100 interneurons, which is consistent with the 10:1 ratio of pyramidal cells to interneurons found in the hippocampus [2]. The intercellular distance is set to 10 micrometers, and the interneurons are equidistantly distributed among the pyramidal cells. Total surface area of a pyramidal cell is set to 50,000 square micrometers, and the total surface area for an interneuron is set to 20,000 square micrometers. The two submodel arrays are considered parallel, and the distance between them is set to 100 micrometers.

**Pyramidal Cell Model**

Pyramidal cells are modeled by the two-compartmental Pinsky-Rinzel model [16]. It is a reduction of the complex 19-compartment Traub model and gives similar results in network simulations. The membrane potential of the soma and dendrite, Vs and Vd respectively, are separately modeled and coupled together according to the following dynamics:



where Cm is the membrane capacitance, and the ionic currents consist of: Ileak, the leak current with conductance gL=0.1 mS/cm2 and reversal potential 0 mV; INa,the sodium current with conductance gNa=30 mS/cm2 and reversal potential 120 mV; IK-DR, IK-AHP, and IK-C, the various potassium currents with respective conductances gK-DR=15 mS/cm2, gK-AHP=0.8 mS/cm2, gK-C=15 mS/cm2 and reversal potential -15 mV; ICa is the calcium current with conductance gCa=10 mS/cm2 and reversal potential 140 mV. ISyn is the current from the synaptic connections on the dendrite only and is divided by the proportion of area taken up by the dendrite (1-*p*), where p is the fraction of area taken up by the soma. Both the soma and dendrite are subject to separate input currents IS and Id divided by the respective area proportions. Finally, the dendritic membrane potential is coupled with the somatic membrane potential via an electronic coupling term gc = 2.1 mS/cm2. The electronic coupling is derived by modeling the soma and dendrite as a cable with length *l*, radius *r*, resistivity *Ri*, and fraction of area *p* dedicated to the soma and 1-*p* dedicated to the dendrite [16].

They synaptic interactions consist of AMPA and NMDA synapses on the dendrite and take the form



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Values used for the synaptic conductances span 0.007 mS/cm2 to 0.014 mS/cm2 according to the simulations done by Pinksy and Rinzel [16].

Some notable features include bursting under steady somatic and dendritic simulation, isolated somatic spikes at high frequencies and isolated dendritic spikes at low frequencies, and low frequency bursts and rapid sodium spikes when the soma and dendrite are intermediately coupled [16].

**Interneuron Cell Model**

Interneurons are modeled by the Wang-Buzsáki model, which consists of a single compartment model voltage dynamics that obey the following [17]:



where the voltage dependent ionic currents (Na and K) are adapted from the Hodgkin-Huxley model in a way that induces brief afterhyperpolarization around -70 mV and high frequency repeated spikes. All the ionic currents resemble those used in the Pinsky-Rinzel model. Isyn resembles a GABA synapse of the form



where the synaptic conductance gsyn is 0.1 mS/cm2 and Esyn is -75 mV. Finally, Iapp represents injected current.

**Results**

**Extension of Model**

Previous work using mathematical hippocampal models does not sufficiently explore the influence of CA1 interneuron-interneuron synapses on SPW-R generation. Using the hippocampal model described previously in this report, we created a network consisting solely of CA1 interneurons. A constant 0.3 nA input current was applied to this network in order to simulate input current from CA3 and CA1 pyramidal cells. We then varied the number of interneurons in the network as well as the probability of a synapse between any two interneurons, and measured the effect on average membrane potential and SPW-R generation. SPW-R generation was quantified by summing the power in the ripple frequency band (110-250 Hz).

**Figures/Conclusions**

In Figure 1 below, the average membrane potential in millivolts over 50 milliseconds was plotted for varying network sizes. A constant 0.3 nA input current was applied, and all other parameters were kept constant, including a constant 0.8 probability of connection between any two interneurons in the network.

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Figure 1: Average Membrane Potential as Function of Network Size

In Figure 1 above, we were curious to see if increasing the number of interneurons in the network would change the overall inhibitory effect such as a decrease in magnitude of the oscillations. As expected, oscillations did appear in all cases, but the overall magnitude stays pretty constant as the number of neurons increased. At best, we can say the magnitude for 1000 neurons looks less than the magnitude for 100 neurons. We would have to verify this by finding the standard error of the mean and comparing confidence intervals.

In Figure 2 below, the average membrane potential in millivolts over 50 milliseconds was plotted for varying probability of connection between any two interneurons in the network. A constant 0.3 nA input current was applied, and all other parameters were kept constant, including a constant network size of 100 interneurons. Blue is a network that has a 0.2 probability of connection between any two interneurons, red has a 0.5 probability, yellow has a 0.7 probability, and green has a 0.9 probability.

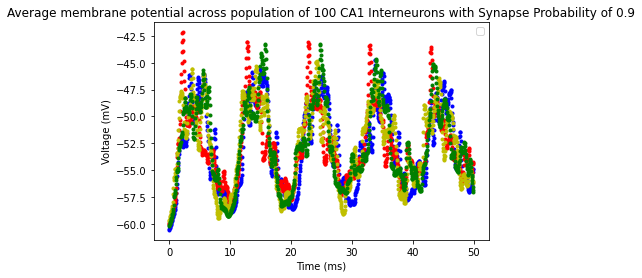


Figure 2: Average Membrane Potential as Function of Connection Probability

From the literature, it seems that synchronized oscillations draw power from how strongly connected a network is, so we were curious to see if the oscillations in Figure 2 would weaken as the connection probability decreased. Unfortunately, we didn’t see much change between low and high probabilities. This could be due to the fact that we are not running the network at the full scale such as 40000 interneurons, which is what is estimated to be in the real hippocampal CA1 area.

In Figure 3 below, the power in the ripple frequency band (110-250 Hz) was summed over 50 ms for CA1 interneuron networks of varying sizes. Power is in units of Voltage^2/Hertz. A constant 0.3 nA input current was applied, and all other parameters were kept constant, including a constant 0.8 probability of connection between any two interneurons in the network.

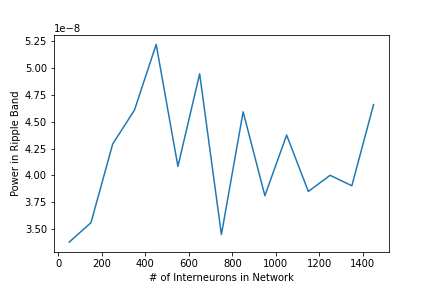


Figure 3: Ripple Band Power as Function of Network Size

In Figure 3 above, the power is very low, and does not significantly increase or decrease as a function of network size. Recalling from the background section, one proposed mechanism for SPW-R generation is that the CA3 pyramidal - CA1 excitation causes interneuron-pyramidal synapses to fire, and the interneurons then force the pyramidal neurons to fire in synchrony. The other was that CA1 pyramidal cells were connected with gap junctions and pyramidal-pyramidal synapses in CA1 generate ripples. Neither of these mechanisms considered the effect of interneuron-interneuron connections in CA1 on ripple generation. We wanted to test this and see if the mechanisms were overlooking these interneuron-interneuron connections. However, this does not seem to be the case from our results. There does not seem to be a significant influence on ripple frequency band power when varying interneuron network size. Perhaps the low power is a result of the limited range of interneurons in our network, as the actual CA1 region contains 40,000 interneurons.

In Figure 4 below, the power in the ripple frequency band (110-250 Hz) was summed over 50 ms for CA1 interneuron networks of varying connection probabilities between any two interneurons. Power is in units of Voltage^2/Hertz. A constant 0.3 nA input current was applied, and all other parameters were kept constant, including a constant network size of 100 interneurons.

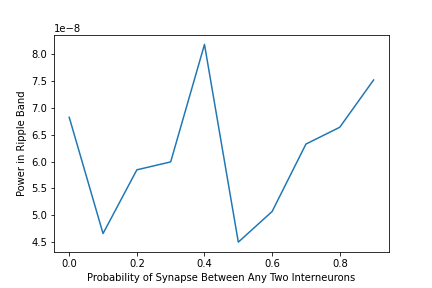


Figure 4: Ripple Band Power as Function of Connection Probability

In Figure 4 above, when other parameters are kept constant, there seems to be an optimal 0.4 probability of connection between any two interneurons in order to maximize ripple band power. However, for all connection probabilities, the power is still very low for our network consisting solely of interneurons. The results from Figures 3 and 4 imply that a network consisting solely of interneurons generates very few SPW-R events, regardless of connection probability and network size. This provides evidence for the necessity of pyramidal cells in SPW-R events, and allows us to tentatively conclude that interneuron-interneuron connections do not have a significant influence on SPW-R generation, when considering a network consisting solely of CA1 interneurons. However, these conclusions are constrained by the limited range of our network size, as the actual CA1 region of the hippocampus contains 40,000 interneurons. We were not able to acquire enough computational power to train networks of this size. Furthermore, if we introduced pyramidal cells into the network, there may be hidden effects of interneuron-interneuron connections that influence SPW-R generation by pyramidal cells.

**References**

[1] Colgin, Laura Lee. "Rhythms of the hippocampal network." Nature Reviews Neuroscience 17.4 (2016): 239-249.

[2] Taxidis, Jiannis, et al. "Modeling sharp wave‐ripple complexes through a CA3‐CA1 network model with chemical synapses." Hippocampus 22.5 (2012): 995-1017.

[3] Squire, Larry R., Craig EL Stark, and Robert E. Clark. "The medial temporal lobe." Annu. Rev. Neurosci. 27 (2004): 279-306.

[4] Cobb, S. R., et al. "Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons." Nature 378.6552 (1995): 75-78.

[5] Aussel, Amélie, et al. "A detailed anatomical and mathematical model of the hippocampal formation for the generation of sharp-wave ripples and theta-nested gamma oscillations." Journal of computational neuroscience 45.3 (2018): 207-221.

[6] Chrobak, J. J., and G. Buzsáki. "Selective activation of deep layer (V-VI) retrohippocampal cortical neurons during hippocampal sharp waves in the behaving rat." Journal of Neuroscience 14.10 (1994): 6160-6170.

[7] Chrobak, James J., and Gyorgy Buzsáki. "High-frequency oscillations in the output networks of the hippocampal–entorhinal axis of the freely behaving rat." Journal of neuroscience 16.9 (1996): 3056-3066.

[8] O’Neill, Joseph, et al. "Play it again: reactivation of waking experience and memory." Trends in neurosciences 33.5 (2010): 220-229.

[9] Karlsson, Mattias P., and Loren M. Frank. "Awake replay of remote experiences in the hippocampus." Nature neuroscience 12.7 (2009): 913-918.

[10] Gupta, Anoopum S., et al. "Hippocampal replay is not a simple function of experience." Neuron 65.5 (2010): 695-705.

[11] Buzsáki, György. "Hippocampal sharp waves: their origin and significance." Brain research 398.2 (1986): 242-252.

hippocampus." Hippocampus 18.9 (2008): 899-908.

[12] Buzsáki, György. "Hippocampal sharp wave‐ripple: A cognitive biomarker for episodic memory and planning." Hippocampus 25.10 (2015): 1073-1188.

[13] Draguhn, A., et al. "Electrical coupling underlies high-frequency oscillations in the hippocampus in vitro." Nature 394.6689 (1998): 189-192.

[14] Ylinen, Aarne, et al. "Sharp wave-associated high-frequency oscillation (200 Hz) in the intact hippocampus: network and intracellular mechanisms." Journal of Neuroscience 15.1 (1995): 30-46.

[15] Both, Martin, et al. "Propagation of specific network patterns through the mouse

[16] Pinsky, Paul F., and John Rinzel. "Intrinsic and network rhythmogenesis in a reduced Traub model for CA3 neurons." Journal of computational neuroscience 1.1 (1994): 39-60.

[17] Wang, Xiao-Jing, and György Buzsáki. "Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model." Journal of neuroscience 16.20 (1996): 6402-6413.