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The Contribution of Relative Activation Levels Between Populations of Cells to Network Activity in a Large-Scale Biologically Realistic Model of the Hippocampus

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Abstract

In previously published work, we showed the progress we've made towards creating a large-scale, biologically realistic model of the rat hippocampus, starting with the projection from entorhinal cortex (EC) to the dentate gyrus (DG). We created the model to help us study how the common components of neurobiological systems in mammals – large numbers of neurons with intricate, branching morphologies; active, non-linear membrane properties; non-uniform distributions throughout membrane surface of these non-linear conductances; non-uniform and topographic connectivity between pre- and post-synaptic neurons; and activity-dependent changes in synaptic function – combine and contribute to give a particular brain region its “neural processing” properties. In this work, we report on the results of a series of simulations we ran to test the role of feed-forward and feedback inhibition in the dentate gyrus. We find that a) the system shows rhythmic bands of activity only in the presence of feedback inhibition, b) that the frequency of rhythmicity increases with increasing amounts of feed-forward inhibition, c) that it decreases with increasing amounts of feedback inhibition, and d) that strong excitatory inputs appear to enhance and prolong the amount of rhythmicity in the system.

I. Introduction

The fundamental building block of neurobiological systems is the neuron, which communicates with other neurons predominantly via electro-chemical signals. The chemical compounds that enable these signals are known as neurotransmitters.

There are many types of neurotransmitters in the brain. Glutamate is the most abundant excitatory neurotransmitter, and is primarily found/contained in projection neurons. GABA, on the other hand, is one of the most common inhibitory neurotransmitters, and is mostly found/contained in interneurons.

In a given brain system, like the hippocampus, a major contributor to the relationship between input and output spike patterns is the balance between excitatory and inhibitory influences on the system. Several factors affect this balance. One is the relative number of

glutamatergic vs. gaba-ergic neurons (the difference between the two is typically large). Another factor is the variety of cell types in the system. A third factor is the number, strength, locations and latencies of the synaptic connections, including both feed-forward and feedback projections.

One of the things our group has been interested in is how feed-forward and feedback inhibition affects network activity in the dentate gyrus, the region of the hippocampus that first processes incoming neural activity. For example, how does the strength of the excitatory input from EC affect granule cell activity? What is the role of basket cell feed-forward and feedback inhibition on granule cell spiking? To answer these questions, we added basket cells, which strongly inhibit activity in the granule cell layer, to our EC-to-DG model and ran a series of simulations in which we varied the strength of the feed-forward and feedback connections.

II. Methods

A. Hardware/Software/Model Components

We are using the same hardware and software configuration as reported previously (1), and refer the reader to that work for the relevant details. We also continue to use granule cells with unique dendritic tree morphologies and multiple non-linear voltage- and ligand-gated membrane channels, connected to by layer II entorhinal cortical cells as constrained by the topography of the system (2). Though we have implemented multiple types of synaptic plasticity (3), we did not include those mechanisms in this set of simulations.

B. Model Structure

In addition to the main excitatory projection from EC to DG, we also implemented the projections from the granule cell population to basket cells, the inhibitory projection from basket cells back to the granule cell layer, and the excitatory projection from EC to the basket cell population. Figure 1 shows the connectivity diagram of the basic circuit, with both feed-forward and feedback inhibitory connections.

III. Results

The first set of results is the baseline dataset, i.e., a simulation that had no inhibition at all. Figure 2 shows the results of this simulation.

With no inhibition at all, notice what you see: there's a strong initial wave of activity in the granule cell population, caused by the onset of entorhinal activity, and followed by spatio-temporal "clusters" of activity. In this case, "spatio-temporal clusters," means that granule cells that are physically near each other are spiking together.

One of the ways we can characterize this data is by doing a population-level frequency analysis on the spike activity, as shown in the plot in the bottom of Figure 2. What you see is a very smooth frequency profile. Most of the strength of the signal is in the lower frequencies (30 Hz and less) with no sudden peaks or valleys in the plot.

Next, when we add inhibition, both feed-forward and feedback, to the model, all of a sudden, we see waves of rhythmic, or synchronous activity, with corresponding peaks in the frequency plots (Figure 3). Generally speaking, these peaks are in the 30–45 Hz range, which puts the activity in the gamma band. Though these plots don't show it, in some cases, the rhythmicity dies out after a few hundred milliseconds, while in other cases, it persists for more than a second or two before finally dying out.

In this particular case, we were experimenting with increasing the strength of the feedback inhibition (Figure 3). As a result, what we see is that as the feedback circuit gets stronger, the frequency of the “waves” decreases – it shifts from a 40 Hz peak to a 35 Hz peak – but becomes stronger and cleaner. So it looks like some kind of modulation is occurring. Also of note is the peak of strong activity less than 10 Hz, which is present in all the data where inhibition occurs.

Next, we move to a set of experiments where we vary the strength of the feed-forward inhibition (Figure 4). What we see here, again, is modulation: as we increase the strength of the feed-forward projection, the frequency of synchrony also increases (there's a shift of the frequency peak from 35 Hz to about 42 Hz), but becomes correspondingly weaker and more filled with noise.

After this, we held constant the strength of both the feed-forward and feedback inhibition while varying the strength of the excitatory input (Figure 5). Our observation here is that increasing the strength of the excitatory connection tends to drive the system to both faster, stronger, and longer lasting oscillations when inhibition is present in the model. In this case, the shift from a 30 Hz, 60 db peak to a 40 Hz, 66 db peak is a fairly strong one.

Finally, we thought we should look at both feed-forward and feedback inhibition in isolation from each other (Figure 6). Here, the left-most plot is the baseline data, showing us network activity in the absence of inhibition – we've seen this already. The middle plot shows what happens when there's feedback inhibition only, while the right-most plot shows network activity with just feed-forward inhibition. As we can see, the feedback-only network shows strong oscillations right around 30 Hz, while neither of the other models have any oscillatory activity to speak of. Also of note are a couple of things occurring in the feed-forward-only network. First, the “clustering” in the granule cells is much denser than in the other two cases. Second, we see a small amount of clustering in the basket cell population. And third, the under-10 Hz frequency peak, which we've seen in many of the other data sets, shows up strongly here (this is the theta band).

IV. Discussion

Summarizing these results, there are a few points to make. First, inhibition is able to cause new types of network activity that otherwise wouldn't exist, namely, the rhythmic banding and the less-than-10 Hz frequency peak that we see. Second, the strength of both the excitatory and inhibitory connections seems to have a modulatory effect on the existing network activity, whether it's to change the frequency, duration, or strength of the rhythmicity. Might these relative connection strengths be a built-in mechanism that the

nervous system has for modulating the various types of activity – namely theta and gamma rhythms – that occur in the hippocampus?

Acknowledgments

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Figure 1.

Model schematic. The diagram on the left shows the high-level connectivity of the system, with inputs from the mEC and IEC enervating both the granule cell and basket cell populations. Both granule and entorhinal cells enervate basket cells, which, in turn, inhibit the GC population.

Figure 2.
top: spike raster plot showing the response of the granule cell population to an input consisting of poisson-distributed broadband noise. Bottom: population-level frequency plot.

Figure 3.

Results from varying the level of feedback inhibition with respect to the amount of both excitatory input and feed-forward inhibition. Increasing feedback inhibition strength decreases frequency of synchrony (peak moves from ~40 Hz. to ~35 Hz. and becomes stronger - ~65 db to ~70 db).

Figure 4.

Results from varying the level of feed-forward inhibition with respect to the amount of both excitatory input and feedback inhibition. Increasing feed-forward inhibition strength increases frequency of synchrony (peak moves from ~35 Hz. to ~42 Hz. and becomes weaker - ~68 db to ~63 db).

Figure 5.

Results from varying the level of excitatory input with respect to the amount of both feed-forward and feedback inhibition. Increasing excitation strength increases both duration and frequency of synchrony (peak moves from ~30 Hz. to ~40 Hz. and becomes much stronger - ~60 db to ~66 db).

Figure 6.

Left: GC spiking activity when there is no basket cell activity. Middle: we see the network activity in the presence of feedback inhibition. Right: network activity in the presence of feed-forward inhibition. Of note is the strong amount of rhythmicity in the middle plot, as borne out by the frequency analysis (bottom).