Presynaptic input synchrony at scale

Linghao Kong[1,*], Heidi Durresi[1,2*], Lu Mi[3], and Nir Shavit[1]

Abstract

We present, for the first time, insights into functional synchronization of individual neurons under a complete anatomical neural connectivity map at a massive scale. While functional synchrony has been extensively studied as a mechanism of information processing in the brain [7], previous work has been limited to small populations of neurons *in vitro* [8], analyses across entire brain regions [5], or simulations *in silico* [4]. Here, we leverage the large scale connectomics dataset MICrONS [1] to analyze synchrony through the proxy of Pearson correlation across neurons at a larger scale *in vivo* with direct anatomic connectivity. We investigate functional synchronization between direct neighbors as a form of Hebbian synchrony, and input synchrony of neurons with a common postsynaptic neighbor.

While synaptic connections significantly increase Hebbian synchrony [3], we find that distance substantially impacts such synchronization. With increasing distance, among both neighbors and non-neighbors, synchronization significantly decreases, reaching almost the same level. For neighbors, such a trend alludes to reasons for maintaining long-range connections other than immediate synchronization. Interestingly, for non-neighbors, this lends further evidence to the role of local, non-synaptic, diffuse signaling mechanisms [2, 9]. Additionally, we find that the number of synaptic connections affects synchronization in a very sharp manner.

For the first time, we show that excitatory postsynaptic neurons exhibit input synchronization *in vivo*, while inhibitory postsynaptic neurons do not. Furthermore, we find that inhibitory postsynaptic neurons are more involved in recurrent connections with their presynaptic neighbors, and hypothesize that these two phenomena taken together could be related to winner-take-all dynamics [6] within excitatory-inhibitory networks. We also observe that presynaptic neurons that have a greater difference in travel distance to the postsynaptic neighbor are less correlated, but that this can be offset by accounting for the relative distance traveled. This suggests that presynaptic neurons time their inputs to a postsynaptic neuron to drive postsynaptic activity more efficiently.

Additional Information

MICrONS. All of our analysis is generated based on the MICrONS connectomics dataset [1]. Briefly, a mouse was shown natural images while Ca^{2+} fluorescence imaging of all excitatory neurons within in a cubic millimeter of mouse visual cortex was recorded. After sacrifice, the same area was imaged with electron microscopy to generate a large scale anatomical connectome. This yields a dataset with both synaptic connectivity and functional data, the first at its scale. The dataset contains information on 200 thousand cells, 75 thousand neurons, and 523 million synapses. We constrain our analysis to the 1600 neurons with their synapses proofread and the 24000 neurons with both functional and anatomical data matched together, in order to guarantee synaptic connectivity and improve accuracy (Fig 1a).

Methodology and Results. We use the Pearson correlation coefficient as a proxy for the degree of functional synchronization in activity of two neurons. Specifically, we keep the maxi-

[*]Equal contribution. [1]Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology. [2]Department of Linguistics and Philosophy, Massachusetts Institute of Technology. [3]School of Computational Science and Engineering, Georgia Institute of Technology.

mum correlation between two neuronal functional traces within continuous sub-windows from their full traces.

To validate our experimental workflow, we first investigate Hebbian synchrony between two neighboring excitatory neurons [3]. We collect pairwise correlations of neighboring neurons, where at least the presynaptic neuron is proofread (Fig 1b). We analyze the relationship between these correlations and the Euclidean distance from the presynaptic to postsynaptic neuron through the synapse. We also pick non-connected control neurons to isolate the effects of synaptic connections. We observe a significantly higher correlation for direct neighbors at all distances, but interestingly both neighbors and non-neighbors have decreased correlations at further distances (Fig 1d). For non-neighbors, such a trend suggests the role of local, non-synaptic signalling that may weakly synchronize nearby neurons [2, 9]. We also find that more synapses between neighboring neurons substantially increases correlation, with a sharp increase at around five synapses (Fig 1f). To our knowledge, this presents the first analysis of Hebbian synchrony at this scale with both functional and structural data.

Because we find such a strong effect of distance on Hebbian synchrony, we repeat this workflow for our experiments on input synchrony. For presynaptic neurons to a proofread neuron, we collect the pairwise correlation between all presynaptic neurons and the Euclidean distance between their cell bodies. Importantly, we do not consider the activity of the postsynaptic neuron at all. As a control, we also select the closest non-connected neuron of the same cell type to each presynaptic neuron. Strikingly, we find that excitatory postsynaptic neurons exhibit input synchronization, while inhibitory postsynaptic neurons do not. Such input synchronization is most apparent for excitatory postsynaptic neurons between relatively close presynaptic neurons (Fig 1g). This represents the first time that this phenomenon has been observed *in vivo* with hundreds of presynaptic neurons of guaranteed structural connectivity. Interestingly, we also find that inhibitory postsynaptic neurons form more bidirectional, recurrent synaptic connections back onto their presynaptic neighbors. Individual inhibitory postsynaptic neurons on average form synapses back onto 26% of their predecessors, as opposed to only 8% for excitatory postsynaptic neurons (Fig 1i). Taken together, we hypothesize that such dynamics are related to winner-take-all computation [6] within excitatory-inhibitory networks, where presynaptic neurons to inhibitory neurons are competing rather than cooperating to propagate signal.

Finally, we look at whether presynaptic neurons account for signal travel time to better drive postsynaptic activity. For two inputs to a neuron, we calculate the difference in distance from their cell bodies to the postsynaptic cell body through their synapse. For presynaptic neurons with more relative distance, their correlation is lower. Interesting, when synaptic travel time is factored in by allowing for a slight offset in the functional traces for all pairs of presynaptic neurons, those further from one another in particular become more correlated, suggesting that such neurons are accounting for travel time (Fig 1h). For direct neighbors, however, accounting for travel time does not increase correlation (Fig 1e). Overall, here for the first time with both functional and structural data, we show that excitatory postsynaptic neurons display input synchronization, while inhibitory postsynaptic neurons do not *in vivo*. We also shed new light on aspects of Hebbian synchrony at scale.

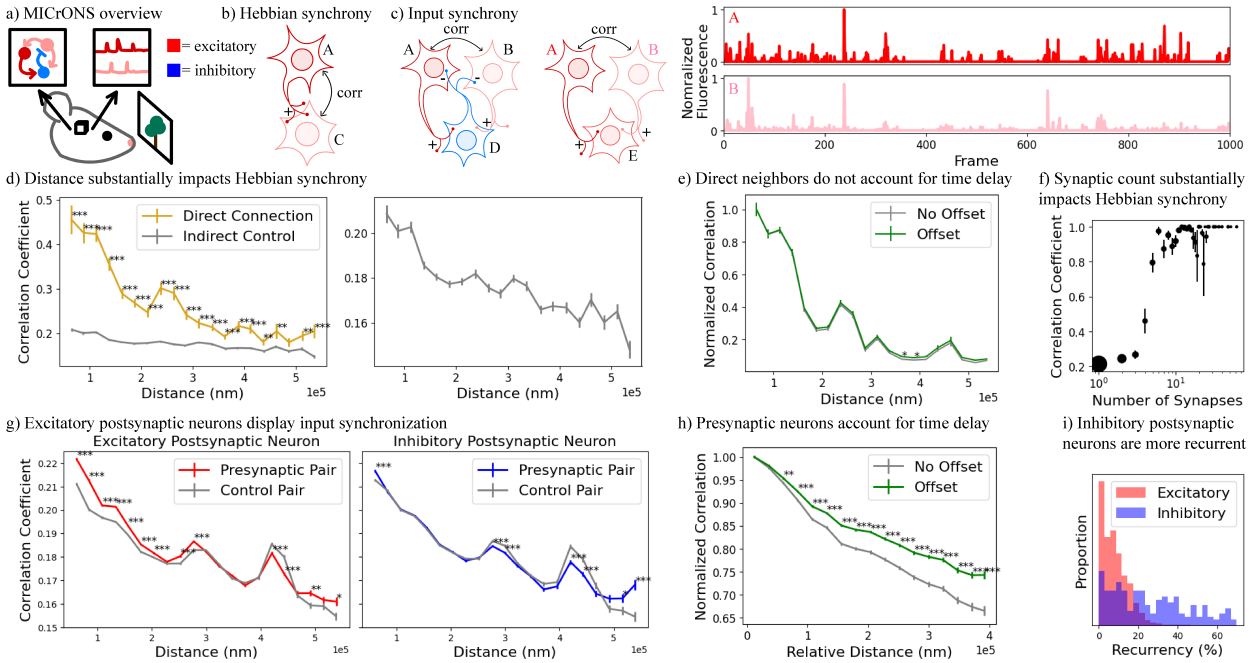

Figure 1: **a)** MICrONS connectomics dataset collection overview. **b)** Hebbian synchrony paradigm between direct neighbors. At least neuron A is proofread. The correlations between neurons A and C are measured. **c)** Input synchrony paradigm between two presynaptic neurons to the same inhibitory (left) and excitatory (center) postsynaptic neuron. At least neurons D and E are proofread. Neurons A and B are not necessarily connected, and their correlations are measured. Representative Ca^{2+} fluorescence intensities of the two presynaptic neurons to neuron E (right). **Hebbian synchrony: d)**, **e)**, **f)**. **d)** Effect of distance on correlation between directly connected neurons (left). Non-connected neurons that are closer are more synchronous (right). **e)** Accounting for synaptic travel time does not increase synchrony between neighbors. **f)** With an increasing number of synapses between neighbors comes a sharp increase in correlation. **Input synchrony: g)**, **h)**, **i)**. **g)** Excitatory postsynaptic neurons show a statistically significant degree of input synchrony (left), while inhibitory neurons do not (right). **h)** Presynaptic neurons with a greater difference in synaptic travel distance are less correlated, but accounting for synaptic travel time increases their relative correlation in particular. **i)** Inhibitory postsynaptic neurons show a greater recurrence. In relevant subfigures, correlations for particular distances are binned, p-values are measured between the distributions at each distance, error bars are one standard error, and ***p<0.001, **p<0.01, *p<0.05.

References

[1] MICrONS Consortium, J Alexander Bae, Mahaly Baptiste, Caitlyn A Bishop, Agnes L Bodor, Derrick Brittain, JoAnn Buchanan, Daniel J Bumbarger, Manuel A Castro, Brendan Celii, et al. Functional connectomics spanning multiple areas of mouse visual cortex. *BioRxiv*, pages 2021–07, 2021.

[2] Kenji Doya. Metalearning and neuromodulation. *Neural networks*, 15(4-6):495–506, 2002.

[3] David Horn, Nir Levy, Isaac Meilijson, and Eytan Ruppin. Distributed synchrony of spiking neurons in a hebbian cell assembly. *Advances in neural information processing systems*, 12, 1999.

[4] Xiaoshen Li and Giorgio A Ascoli. Effects of synaptic synchrony on the neuronal input-output relationship. *Neural computation*, 20(7):1717–1731, 2008.

[5] Stefanie Liebe, Gregor M Hoerzer, Nikos K Logothetis, and Gregor Rainer. Theta coupling between v4 and prefrontal cortex predicts visual short-term memory performance. *Nature neuroscience*, 15(3):456–462, 2012.

[6] Nancy Lynch, Cameron Musco, and Merav Parter. Winner-take-all computation in spiking neural networks. *arXiv preprint arXiv:1904.12591*, 2019.

[7] Michael Okun, Nicholas A Steinmetz, Lee Cossell, M Florencia Iacaruso, Ho Ko, Péter Barthó, Tirin Moore, Sonja B Hofer, Thomas D Mrsic-Flogel, Matteo Carandini, et al. Diverse coupling of neurons to populations in sensory cortex. *Nature*, 521(7553):511–515, 2015.

[8] Charles F Stevens and Anthony M Zador. Input synchrony and the irregular firing of cortical neurons. *Nature neuroscience*, 1(3):210–217, 1998.

[9] ES Vizi, A Fekete, R Karoly, and A Mike. Non-synaptic receptors and transporters involved in brain functions and targets of drug treatment. *British journal of pharmacology*, 160(4): 785–809, 2010.