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Large-scale synapse-level neuronal wiring diagrams in silico and in vitro

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Introduction

Neuronal network function is likely to depend on single synapse details, but reconstructing wiring diagrams with single synapse precision is difficult to do on a large scale. We describe a method for circuit reconstruction on a large scale by using high-throughput but low-resolution readouts such as somatic calcium recordings and extracellular electrical recordings. We propose that these techniques may scale very well using new optical recording and stimulus techniques, and enable large-scale yet precise circuit reconstruction.

Computational methods

We used network simulations of 10,000 input neurons and 100 output neurons. This network was loosely based on the mammalian hippocampal CA3 to CA1 circuit. The CA3 input neurons were modeled as single compartments. The CA1 output neurons used 19-compartment models based closely on [1] with voltage-gated Na^+, Ca^{2+} and K^+ conductances, as well as calcium pools and Ca^{2+}-activated K^+ channels. Later simulations used more detailed compartmental models [2]. Simulations included variability in neuronal properties, stochasticity of synaptic release, and readout noise. Simulations were done using GENESIS and MOOSE and run on an Opteron Linux cluster from Sun Microsystems.

Experimental methods

We used the rat hippocampal brain-slice preparation and standard media and recording conditions. CA1 neurons were labelled using ballistic loading of calcium green fluorescent dye. Single-cell responses were optically recorded using an ANDOR EMCCD camera. Stimuli were given using an array of bipolar electrodes.

Results

By using a strong baseline stimulus to activate several input axons (in silico and in vitro) we elicited action potentials and calcium signals at the CA1 neuronal soma. To resolve single synapses we added a minimal strength 'probe' stimulus on another electrode, so as to activate one or a few axons. With ~80 repeats we were able to discriminate the distributions of the calcium signals from the baseline and the probe+baseline cases. In the simulations we showed that this distribution shift reported the presence of the synapse with 20 to 50% success and very few false positives. Electrical readouts, having high time-resolution, resolved even more synapses. In the experiments we found such putative synapses on approximately 20 to 30% of the input-electrode/readout neuron pairs, which was consistent with the simulation prediction for near-minimal stimulation.

Conclusion

We show using models and experiments that we can use low-resolution recording methods with an array of stimulus points to obtain connection matrices with single synapse resolution in living networks.

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References

1. Traub RD, Wong RK, Miles R, Michelson H: **A model of a CA3 hippocampal pyramidal neuron incorporating voltage-clamp data on intrinsic conductances.** *J Neurophysiol* 1991, **66(2):**635-650.
2. Bhalla US: **How to record a million synaptic weights in a hippocampal slice.** in press.