Studying evoked potentials in large cortical networks with PGENESIS 2.4

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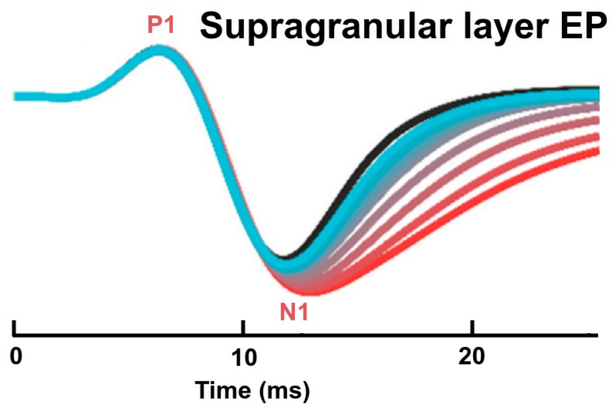
Introduction and Goals

GOALS: (1) Understand how inhibition of pyramidal cells (PCs) by basket cells (BCs) affects the shape of evoked potentials (EPs) in a region of neocortex. (2) Implement a large cortical network model on parallel supercomputers.

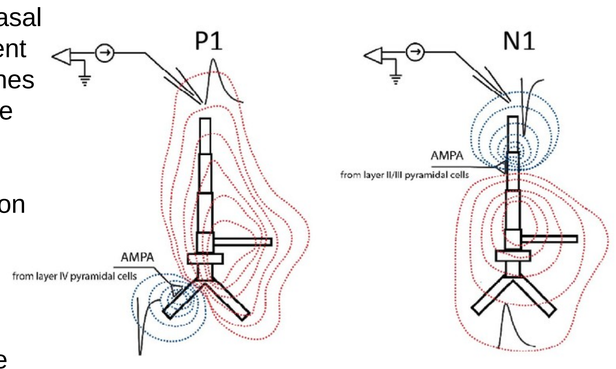
The figure shows results [1] when EPs were recorded from rat barrel cortex and a GABA antagonist was applied to vary the amount of inhibition. It shows that decreasing inhibition (dark red) widens N1, but has no effect on P1 or the initial portion of N1.



The ACnet2 model of primary auditory cortex (AI) [2] has been used to reproduce and understand adaptation by Kudela, et al. [3], as measured by cortical surface electrodes in an 'oddball paradigm' experiment. They also found that both the vertex-positive P1 peak in the auditory EP and the vertex-negative N1 peak arise from excitatory currents in the pyramidal cells (PCs). This is illustrated in Figure 4 from the paper.

LFP traces (black) show response to excitatory synaptic current inputs (sinks) injected into the basal (left) and apical (right) dendrite of a 9-compartment layer 2/3 model of a PC. Red and blue contour lines correspond to positive and negative values for the LFP amplitude, respectively.

Features of the EP are explained by the orientation of electric dipoles that are formed when synaptic currents enter or leave the cell at one point and compensating leakage and capacitive return currents flow through other dendrite sections. P1 arises from excitation at the basal dendrite and N1 at the apical dendrite.



Morphology Matters! These results show that:

Accurate modeling of neural activity, including EPs recorded from scalp or cortical surface electrodes, requires multi-compartmental neuron models with enough realism in the dendritic morphology and location of synapses to account for the major sinks and sources of currents in the extracellular medium.

GENESIS and PGENESIS

Modern neural simulators have been developed for large scale network models of single-compartment integrate-and-fire neurons that can efficiently model millions of neurons. However, the GENESIS and NEURON simulators, both developed over 30 years ago, are the only ones currently capable of providing this degree of morphological realism for large network models.

From the beginning, GENESIS was designed for creating realistic models of cortical networks of multi-compartmental neurons, and to eventually be used on parallel computers.

GENESIS is implemented with an object-oriented design that groups related object and command definitions into separately compiled libraries. Parallel GENESIS (PGENESIS) adds a library with a "postmaster" object to the usual GENESIS objects and commands. This allows a GENESIS simulation (e. g. a large network model) to be split into many MPI processes that communicate through the postmaster. When sufficient CPU cores are available, each process can be assigned to a separate core.

This object-oriented design and organization not only fosters the community development of neural models, but of the simulator itself. Recent updates to the November 2014 release of GENESIS 2.4 through the Repository for Continued Development of the GENESIS 2.4 Neural Simulator (https://github.com/genesis-sim/genesis-2.4) have been incorporated into a new mutually-developed release of PGENESIS 2.4.

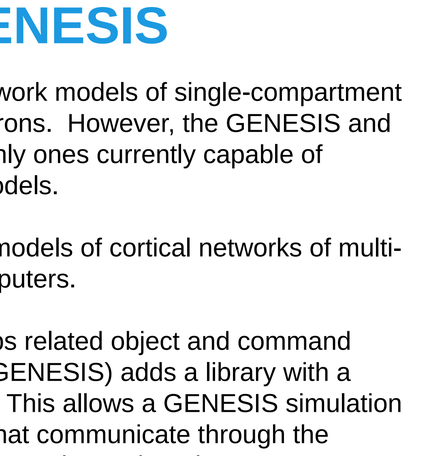
PGENESIS 2.4 on Supercomputing Resources

Crone, et al. [4] and a group at the U. S. Army Research Laboratory have modified the older 2006 release of GENESIS and PGENESIS 2.3 to allow simulations of networks of up to 9 million neurons. Their modifications addressed memory management and other issues that limited model scalability on high performance computing (HPC) resources.

Rapidly increasing memory usage with model size was a significant limitation of the previous PGENESIS. Integration of the Boehm-Demers-Weiser garbage collector (www.hboem.info/gc/) into PGENESIS dramatically reduced the memory used per core with increasing model size.

Using the modified version of PGENESIS 2.4 and a thalamocortical network model as a benchmark, simulation performance and scalability was evaluated. The benchmark model contained 12 different types of neurons (e.g., pyramidal cells, interneurons, etc.). Different neuron types had between 50-74 compartments. We demonstrate that with HPC resources, we can tractably simulate high fidelity neural networks with 9 x 10^6 neurons at 2,000 connections per neuron (18 x 10^9 synapses)

The updated PGENESIS 2.4 is now available for running large-scale network simulations on supercomputers at the Neuroscience Gateway Portal (NSG) [5] at https://www.nsgportal.org.



The auditory cortex model

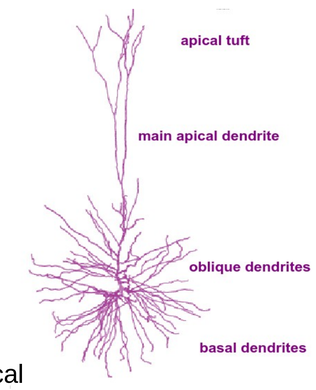
We used the new PGENESIS to simulate EPs measured 2 mm above a patch of layer 2/3 primary auditory cortex. This single-layer version of the model in [3] uses 2304 17-compartment pyramidal cells (PCs) based on human cortical PC reconstructions [6] and 576 simple basket cell (BC) models.

1. Short tone pulses produce excitation to PC distal basal dendrites, as if they were coming from layer 4, as in the multi-layer version of the model.

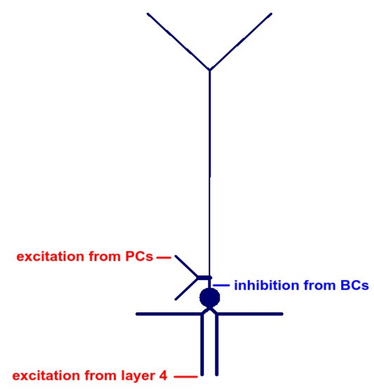
2. Subsequently, PC-PC mutual excitation occurs at oblique apical dendrites.

3. PCs excite the BCs.

4. BCs then inhibit PCs at the proximal apical dendrite.



Human PC (Eyal et al 2016, Fig 1c4)



17 compartment model

The fast GENESIS "hsolve" solver was used on each cell to provide highly efficient spike distribution. Two new hsolve-compatible GENESIS objects are used to provide short term synaptic depression or facilitation and to properly calculate field potentials, using all transmembrane and capacitive currents.

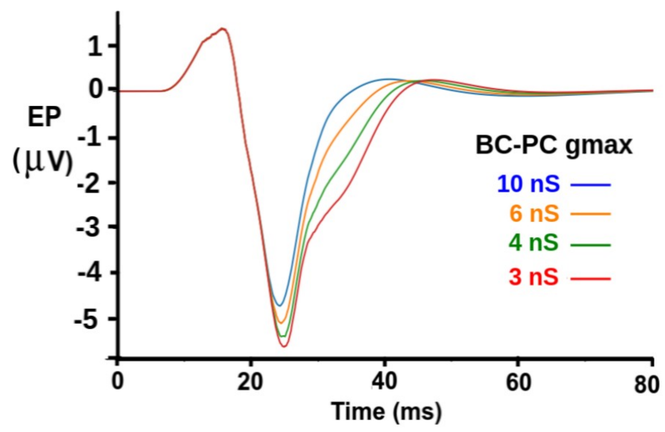
For the PGENESIS implementation, the network was divided into 24 slices simulated in parallel. These, and two processes for input and output, were assigned to 26 processor cores on the Comet XSEDE supercomputer through the NSG portal.

Results

EPs shown were calculated from a trial-averaged sequence of short 1000 Hz tones.

It was shown in [3] that the two currents from the initial excitation and the PC-PC mutual excitation produce oppositely oriented electric dipolar charges that are responsible for the initial vertex-positive P1 peak and the following vertex-negative N1 peak in the EP.

These results show the effect of varying the strength of the inhibition at the PC proximal apical dendrite from BCs. Inhibition onset occurs later in the N1 peak, and produces a dipole that is oriented oppositely to the one that causes the N1 peak. Therefore, decreasing the maximal inhibitory conductance widens the latter part of N1, with minimal effect on P1.



Conclusions

We have shown that a network with a simplified but structurally realistic human layer 2/3 PC model can adequately reproduce the effects of BC inhibition on EPs. This requires that it have sufficient basilar membrane area to allow the inward return currents to occur below the outward inhibitory currents.

With the new PGENESIS available on [5] and other supercomputer resources, we hope to foster collaborations for using realistic network models to understand human cortical activity.

Future Plans

Rescale the model to human AI - The original model was based on measurements in mouse and cat AI and had an artificially low cell density in order to reduce computational requirements.

This requires an increase in the model size and cell density.

Expand the model to both layers 2/3 and 5/6:

This single-layer network shows a similar adaptation as the two-layer model [3], in which layer 2/3 receives depressing synaptic input from layer 4 PCs. Combining the two models is the next step, before adding connections to a layer 5/6. Recurrent connections between the layers may influence patterns of excitation and inhibition in the network as a whole, affecting the shape and position of EP components.

All of the above require large-scale models, implemented with PGENESIS on supercomputers.

How to get PGENESIS 2.4 and the model

This combined official release of PGENESIS 2.4 and updated GENESIS 2.4 is now available from the GENESIS web site (http://genesis-sim.org).

The ACnet23 model with instructions for running it on NSG will be available on genesis-sim.org and ModelDB in Fall 2019.

References

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