

# Epileptiform Activity Patterns in Coupled Neuronal Networks

Hyong Lee<sup>1</sup>, Mark Hereld<sup>2,3</sup>, Rick Stevens<sup>2,3</sup>, Wim van Drongelen<sup>1,3</sup>

<sup>1</sup>Department of Pediatrics, University of Chicago, IL, USA

<sup>1</sup>Department of Mathematics & Computer Science, Argonne National Laboratory, IL USA

<sup>3</sup>Computation Institute, University of Chicago, IL, USA

**Abstract**—We evaluate occurrence of seizure-like activity in computational network models based on the histology of mammalian cortex. In the simulations, seizure onset activity in a network (active patch) is connected to a larger patch of cells (passive patch). The following scenarios were investigated: (1) the active- and passive patches are contiguous with all connectivity intact; (2) active and passive populations are separated ( $\geq 1$ mm interdistance) with long-range connectivity dominating between them. We find that linking the active patch with a passive patch of sufficient excitatory susceptibility reduces pathological network bursting behavior otherwise present in the active patch, even over a separation of several mm. In addition, the balance of excitatory and inhibitory strength in the passive patch plays a crucial role in its ability to restrain network bursting in the active patch: unexpectedly, if the activity in the passive patch is too low, then the active patch can drive network bursting in both patches.

**Keywords**—Network Model, Epilepsy, Parallel Computing

## I. INTRODUCTION

About 1% of the world’s population suffers from epilepsy, a neurological disorder characterized by chronic seizures. About 30% of patients with epilepsy are not adequately controlled with anticonvulsants [1]. The electroencephalogram (EEG) recorded during epileptic seizures frequently shows a sustained oscillatory pattern with sudden onset and offset. The neural mechanisms underlying this oscillatory EEG activity are not well understood, and the experimental techniques to alter and explore functional properties of individual neurons or small networks during seizures are limited.

Here, we evaluate epileptiform network activity of smaller populations of several thousands of neurons in a computational model. This approach has the advantage that functional parameters can be easily manipulated at both the scale of the individual neurons and at the network level. In previous work we described how seizure-like patterns can arise in networks  $< 10^3$  neurons [2, 3]. The purpose of this study is to examine propagation of this type of epileptiform activity in a larger neuronal population.

## II. METHODS

In our neocortical model we include excitatory and inhibitory neuronal populations, each consisting of different

cell types. The excitatory network consists of superficial deep pyramidal cells. Inhibitory interneurons receive input from both types of pyramidal neurons. Gap junctions between inhibitory cells show nearest neighbor connectivity. The implemented inhibitory interneurons are three types of basket cells and the chandelier cell. In a short range, the synaptic connectivity decreases with distance between source and target elements. At the intermediate and long range ( $> 1$ mm and up to a cm scale), connections create a so-called small-world network. The model was implemented on the pGenesis neural simulation environment [4] and run on Jazz, a 350-node Beowulf cluster located at Argonne National Laboratory. Details of how the model was constructed have been published [2, 3, 5].

The cells in the model network (2532 neurons) were subdivided into contiguous “active” and “passive” patches. All neurons contain fast sodium and delayed rectifier potassium channels. In the active patch ( $1/4$  of the total cells), 30% of the superficial pyramidal cells also possessed persistent sodium channels; the passive patch ( $3/4$  of the total cells) had none. These persistent sodium channels are associated with bursting behavior, a type of cellular behavior that was found present in focal tissue of patients with epilepsy [6]. A number of simulations, in which the distance between the two patches was varied between 0 (one single contiguous patch, Fig 1a) and 100 mm (two almost independent patches, Fig. 1c), were performed. Except for the geometrically contiguous case, the distances were large enough that the connections between the two patches would be dominated by long-distance fast connections.

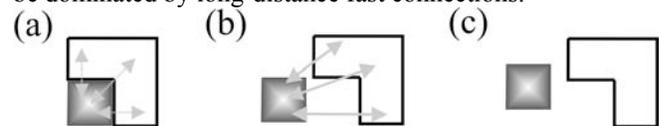


Fig. 1. Overview of the simulation scenarios. (a) a contiguous patch, (b) two patches separated by a distance in the order of several mm, and (c) two almost independent patches at a distance of  $\geq 100$  mm.

The behavior of the patch was monitored by observing the activity of the superficial pyramidal cells, and also via a weighted sum of cellular membrane potentials designed to parallel the behavior of extracellular microelectrodes. The simulations began with both patches at the same excitatory and inhibitory synaptic strengths. The excitatory synaptic strength of the active patch was *reduced* from its initial level to a very low value during the first 6 seconds of the simulation, and then held constant at this low value for the final 4 seconds. The synaptic strengths of the passive patch were held constant over the entire run. This was done to

assess the overall response of the network when a subset of the cells transitioned to a region of abnormal behavior corresponding to seizure onset.

### III. RESULTS

The simulation run with 100 mm separation showed the two patches' intrinsic behavior. Fast oscillations in the "microelectrode" of the active patch early on in the simulation gave way to network bursting initiated by the spontaneous bursters at later times; the passive patch showed no activity when disconnected from the active patch. At 3mm separation, the active patch was able to drive high-frequency oscillations in the passive patch. The frequency of the oscillations in the passive patch went down slightly ( $\sim 30$  Hz to  $\sim 20$  Hz) as the active patch began to display network bursting, but the passive patch continued to oscillate with roughly the same amplitude. In the active patch, however, the additional activity induced by the interaction with the passive patch significantly reduced the amplitude of the network bursting behavior. Figure 2 shows a snapshot of the active and passive patch behavior at a separation of 3mm. Finally, when the two networks were made contiguous, the active and passive patches exhibited high frequency ( $\sim 30$  Hz) oscillations but the active patch did not show obvious bursting in its overall behavior. We also explored the reaction of the contiguous patch to changes in synaptic coupling strength. We found that increasing the

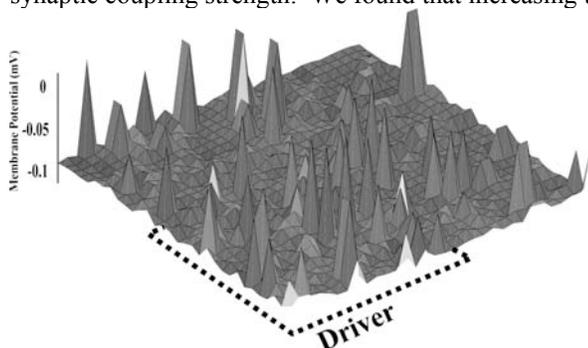


Fig. 2. Snapshot of an activity pattern in the superficial pyramidal cell layer. Here the active (or driver) patch (lower corner) entrains the passive (or driven) patch at a distance of 3mm (scenario in Fig. 1b).

strength of inhibitory synaptic coupling made the patch overall behave more like the spontaneous bursters.

### IV. DISCUSSION

The simulated epileptiform activity indicates that a separation of several mm between the driving and driven networks may facilitate propagation. An isolated network that loses excitatory strength seems to allow bursting cells to dominate overall network activity. When such a network is incorporated in a 'healthy' population of neurons this epileptiform activity does not occur, perhaps due to excitation from the surroundings. When the link between

active and passive networks is made weaker, the epileptiform activity reappears and then propagates to the neighboring network via the long-range, fast connections.

Current opinion in epilepsy research is that over-excitation and lack of inhibition are associated with epileptiform activity [7]. The simulation results presented here indicate that the typical excitation-inhibition balance scenario is oversimplified when discussing networks containing spontaneously active cells. We believe the results are more easily understood in terms of a competition between the relatively simple bursting behavior of the spontaneously active cells and the more complex response of the rest of the network. If the network is quiet enough for the spontaneous bursters to dominate behavior, then pathological network bursting results. If, on the other hand, the rest of the network exhibits enough complexity in its response to make the spontaneous bursters only one set of the many voices in the mix, then the overall patch can succeed in preventing the highly disruptive network behavior shown by the bursters in isolation -- not only itself, but in the abnormal subnetwork as well.

### ACKNOWLEDGMENT

This work was supported by a Falk Grant and the US Department of Energy, Contract W-31-109-ENG-38.

### REFERENCES

1. P. Kwan and M. J. Brodie, "Early identification of refractory epilepsy," *N. Engl. J. Med.* Vol. 342, pp. 314-319, 2000.
2. W van Drongelen W, H. C. Lee, H. Koch, F. Elsen, M. S. Carroll, M. Hereld, and R. L. Stevens, "Interaction between cellular voltage-sensitive conductance and network parameters in a model of neocortex can generate epileptiform bursting," presented at the 26<sup>th</sup> Annual Conference IEEE Engineering in Medicine and Biology Society, San Francisco, CA, IEEE Catalog No: 04CH37558C, ISBN: 0-7803-8440-7; pp. 4003-4005a, 2004.
3. W. van Drongelen, H. C. Lee, M. Hereld, Z. Chen, F. Elsen, and R. L. Stevens, "Emergent epileptiform activity in neural networks with weak excitatory synapses," *IEEE Trans. Neur. Sys. & Rehab.*, in press.
4. J. M. Bower and D. Beeman, *The book of GENESIS*. New York: Springer, 1998.
5. W van Drongelen, H. C. Lee, M. Hereld, D. Jones, M. Cohoon, F. Elsen, M. E. Papka, and R. L. Stevens, "Simulation of neocortical epileptiform activity using parallel computing," *Neurocomputing* vol. 58-60, pp. 1203-1209, 2004.
6. W. van Drongelen, H. Koch, F. Peña, A. Tryba, M. Parkis, J. Loweth, K. E. Hecox, M. Kohrman, D. Frim, M. S. Chico, J-M. Ramirez, and C. J. Marcuccilli, "Differences in bursting properties between least and most abnormal tissue obtained from pediatric patients with intractable epilepsy," presented at the Society for Neuroscience Conference Program No. 99.15.2003 Abstract Viewer/Itinerary Planner. Washington DC: Society for Neuroscience, 2003.
7. A. V. Delgado-Escueta, W. A. Wilson, R.W. Olsen, and R. J. Porter, "New waves of research in the epilepsies: crossing into the third millennium," in *Advances in Neurology* vol. 79: Jasper's Basic Mechanisms of Epilepsies, A.V. Delgado-Escueta, W.A. Wilson, R.W. Olsen, and R.J. Porter, Eds. Philadelphia: Lippincot, Williams & Wilkins, 1999, pp. 3-58.