Simulating the spread of activation in neocortical circuits

SA Neymotin[1], JC Wester[2], D Contreras[2], WW Lytton[1,3,4,5]

SUNY Downstate/NYU-Poly BME Program (1), U. of Pennsylvania, School of Medicine (2), SUNY Downstate Dept. Phys. & Pharm.(3), Neurology(4), Kings County Hospital(5)

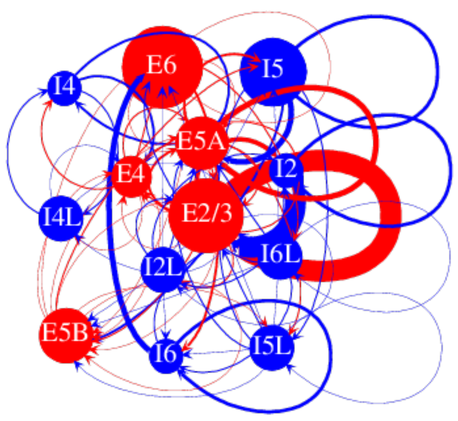
Introduction

Epilepsy is a complex dynamical disease involving multiple scales across time and space. Complex dynamics make prediction difficult. We developed a small model of sensory neocortex that replicated neocortical dynamics. We then augmented connectivity in the model to produce seizure-like spread of activity. Finally, we tested the effectiveness of simulated ablations and targeted stimulations in reducing the spread and initiation of seizures.

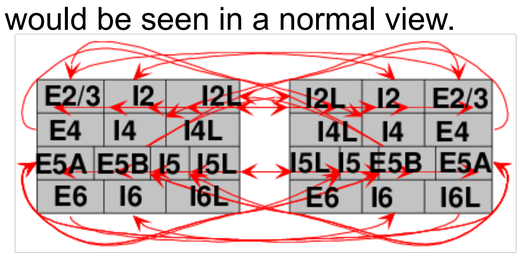
Methods

Layout of the model

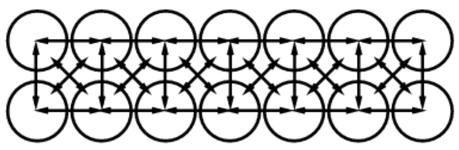
Intracolumnar connections: Red are excitatory (E) populations (circles, size represents population size) and projections (lines, width represents projection strength); blue for inhibitory (I).



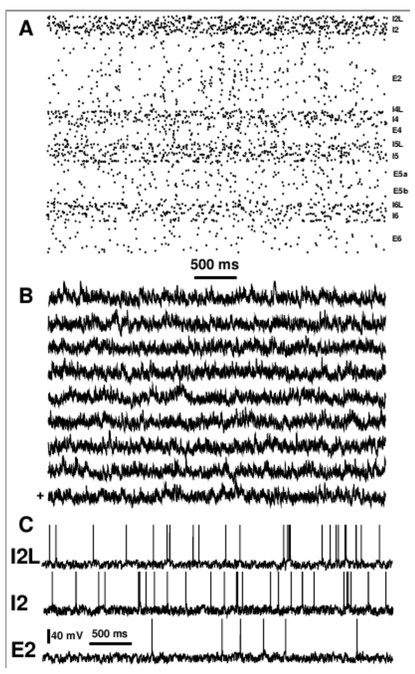
Intercolumnar connections: Layers are here explicitly represented as would be seen in a normal view.



Tangential view looking down to show connectivity of columns in a 2×7 model.



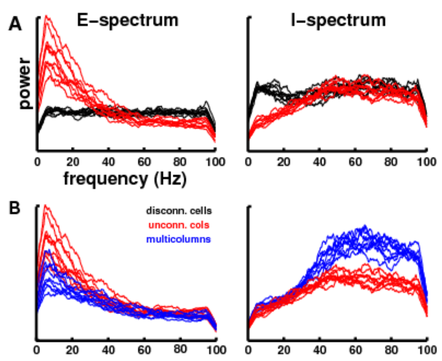
Multiscale network activity



Results

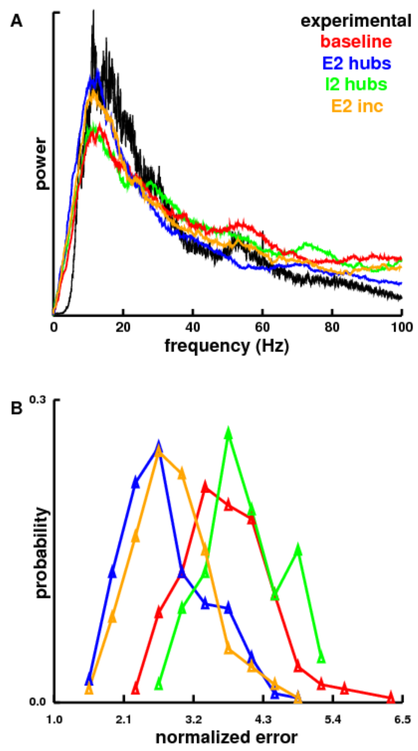
Spectral peaks emerge from cell-cell interactions in network.

Connecting the cells into the individual columns(red) produces a large theta peak in E-cells and a broad gamma peak in I-cells.

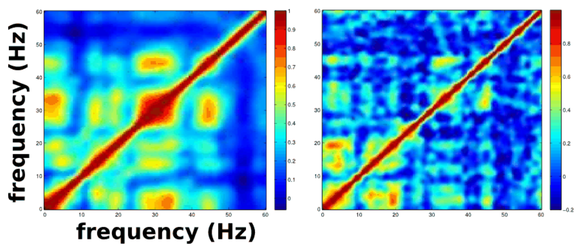


Comparison with experimental data

Comparison of power spectra from LFP recorded in left medial prefrontal cortex of awake rat to normalized MUA power spectra from different simulation types.



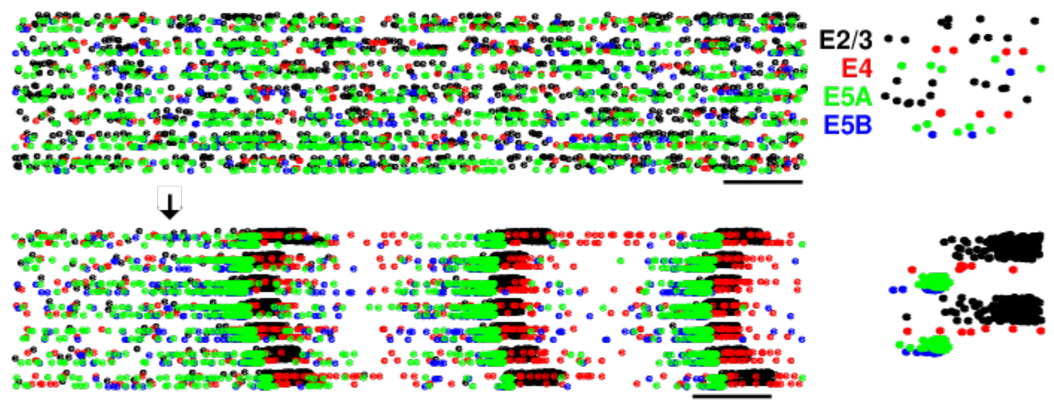
The frequencies that show coupling, and those that don't, are similar in both experiment and simulation.



Spectral power correlations from LFP of awake rat (medial prefrontal cortex; left) and simulated excitatory MUA (right). Additional simulations demonstrated that pattern emerges from interaction of E generation of theta with I sculpting of gamma.

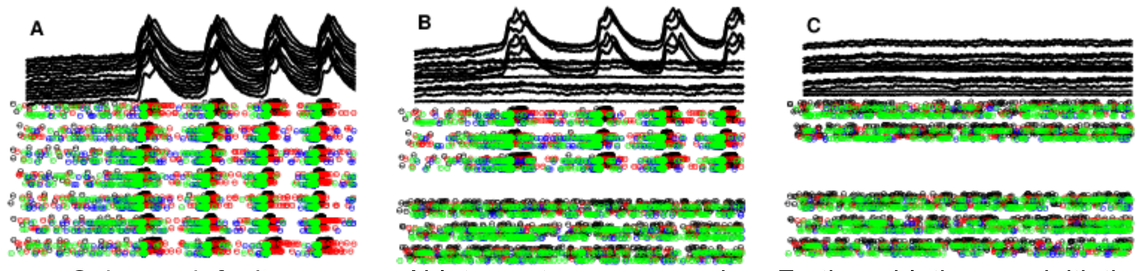
Spontaneous emergence of seizures after *hyper*-connectivity between E cells

Top: Raster plots of baseline activity. Each dot (color code to right) represents a single spike from an excitatory cell. Scale bar 25 ms is time of detail at right, taken from lowest trace. Note that each y location is a different cell.
Bottom: E transition to epileptic activity.



Blocking activation by focal ablation

Reduce spread or eliminate seizure in 2 × 7 model. Each trace is 500 ms in duration. LFPs at top, shown in order of the rasters at bottom, start slightly after the rasters due to an edge effect.



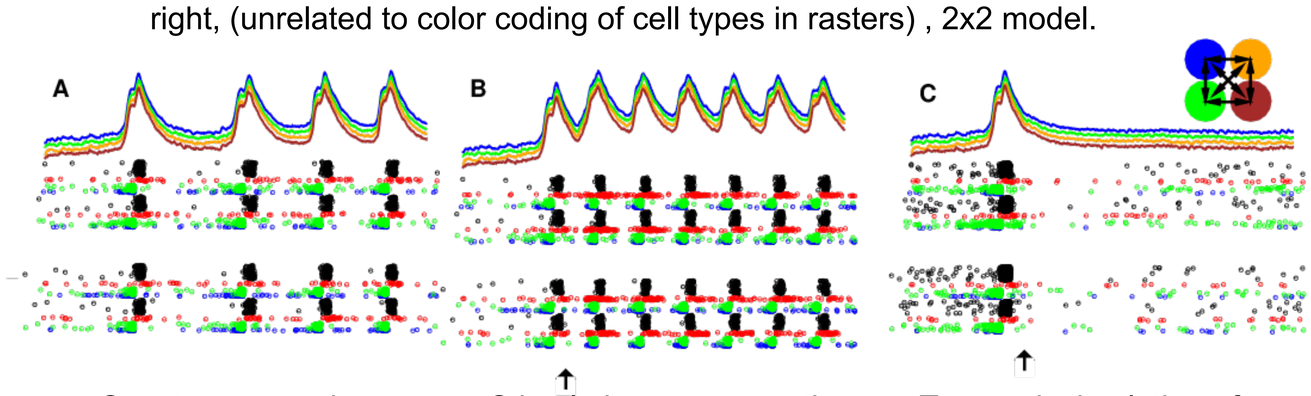
Seizure: default

Ablate center->no spread (trivially since no connect)

Further ablation->no initiation

Blocking activation by focal stimulation

Stimulation to stop seizure. Each trace 500 ms. LFP color code at upper right, (unrelated to color coding of cell types in rasters) , 2x2 model.



Spontaneous seizure in 2x2 model

Stimulation->no cessation via post-interictal spike refractory period

Targeted stimulation of interneurons-> shut-down spread and terminate seizure

Conclusions

1. Realistic pattern of firing frequencies and frequency relationships emerge from a relatively simple multicolumnar network.

2. Epileptic seizures might develop with relatively small increases in inter- and intracolumnar connectivity between excitatory cells and then spread between columns via connections through layers 5 and 2.

3. Targeted microablation could prevent activation or spread of seizures.

4. Optogenetics would offer advantages over electrical microstimulation in terminating seizures or reducing seizure spread and may be an effective treatment for preventing seizure initiation *in-vivo*.

Research supported by DARPA N66001-10-C-2008 and NIH R01MH086638
Acknowledgments: Andre Fenton (NYU), Heekyung Lee (SUNY Downstate), Larry Eberle (SUNY Downstate)