Circuit changes augment disinhibited shock responses in computer models of neocortex

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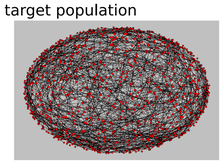
There is limited knowledge and some disagreement regarding the density of connections between cortical layers. There is still less known about connectivity within each layer. In the absence of definite knowledge, modeling allows us to test hypotheses about cortical wiring and dynamics in-silico.

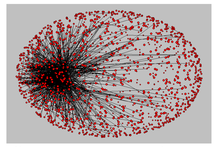
Graph Methods

Network setup: Graph measures will differ depending on how we connect cells within or between layers. Since the basic models give densities but not distributions, we tried 4 different distributions:

1. Uniform: each cell connects randomly to any other cell in target population



2. Scale-Free: most cells have few connections, but a few hubs connect to most other cells



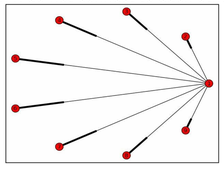
3. Fixed: Divergence is fixed for each cell; convergence varies.
4. Normal: Divergence follows normal distribution.

Measures:

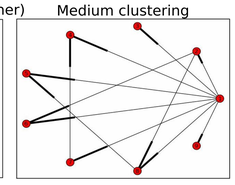
Standard neurobiological connectivity measures -- divergence, convergence, connection density -- are complemented by layer-specific or cell-specific graph-theoretic measures in order to characterize cortical wiring. 3 major graph-theoretic measures were used:

1. Clustering coefficient: How likely are neighbors of a cell to be connected to each other? A cluster is similar to a Hebb cell assembly.

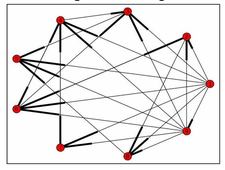
No clustering (cells connected to cell on R do not connect to each other)



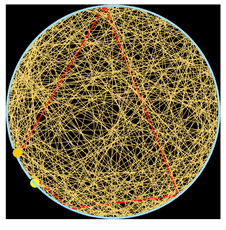
Medium clustering



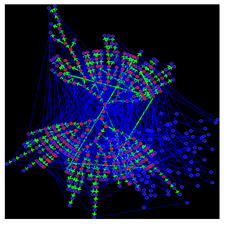
High clustering



2. Path length: average of shortest paths to connect two units. "Path" in graph theory is # of edges between nodes (cells) crossed to get from node A to node B. The path length shown below is 4.



3. Centrality: how many shortest paths does a cell lie on?

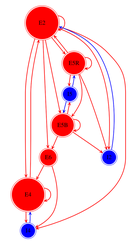


4 models all show Layer 2/3 dominance

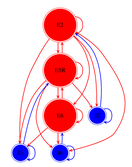
Automated graph analysis of 4 published cortical models. L2/3 (E2) is a central hub. Reciprocal excitatory feedback between L5 (E5) and L2/3 provide the next level of interaction for activating epileptiform activity.

Red=excitatory. Blue=inhibitory. Size of circles proportional to # of cells. Straightness of edges proportional to density of connections. Length of edges inversely proportional to density of connections. Circles sorted top to bottom by total average divergence.

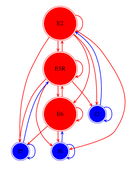
Primary Visual Cortex (based on Martin model [4,6,7,10])



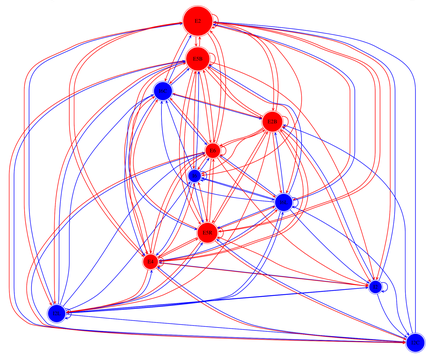
Primary Visual Cortex (based on Franaszczuk model [2])



Primary Motor Cortex (based on Tononi model [8,12])



Auditory Cortical Column (based on Traub model [24])



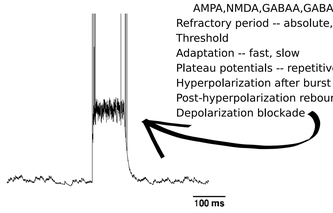
Acronym Key: E=excitatory; I=inhibitory; L=layer. E2 are excitatory cells in layer 2/3 (2 is short for L2/3); most E cells are pyramids; most I cells are basket cells; I2O are double bouquet cells which may be in L2/3 or L5; I2C, I4, I6C are chandelier cells;E4 are spiny stellate cells; B in E5B,E2B=bursting, R in E5R=regular firing; L in I2L,I6L=LTS=low threshold spiking (bursting and LTS not currently explicitly implemented)

Dynamics

We're interested in which wiring predisposes to sustained activity (ictal activity). So far we have only explored the Martin model. Some wirings show sustained activity. Initial stimulus is to E4 and E6 (thalamocortical inputs)

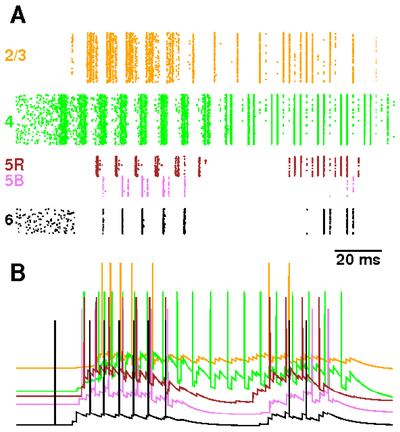
Cell model

Event-driven rule-based unit model (I&F+):
- Different types of synapses: AMPA,NMDA,GABAA,GABAB
- Refractory period -- absolute, relative
- Threshold
- Adaptation -- fast, slow
- Plateau potentials -- repetitive firing
- Hyperpolarization after burst
- Post-hyperpolarization rebound
- Depolarization blockade



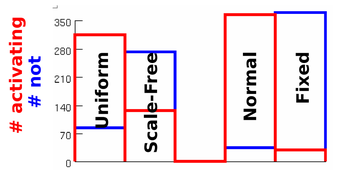
Network model

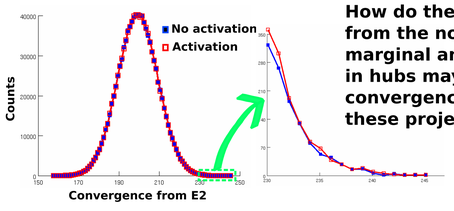
Stimulation to layers 4,6 lasting 20 ms. Activity spreads across layers. All E cells in network are shown in raster.



Haven't solved problem of balancing weights so as to get 50/50 active/not-active. Here we use different connectivity algorithms (within or between layers) but do not get near this balance (33/66 for scale-free case). We may need to use an adaptive algorithm to set weights. (See Poster Column 1 for description of the 4 distributions used.)

1600 simulations run

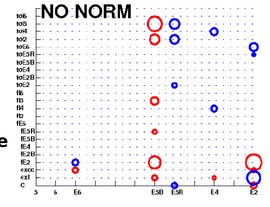




How do the activated networks (red) differ from the not-activated (blue). Differences are marginal and subtle -- ie a small increase in hubs may make a big difference. Here we look at convergence from E2/3 cells for all units to which these project -- no clear conclusion possible here.

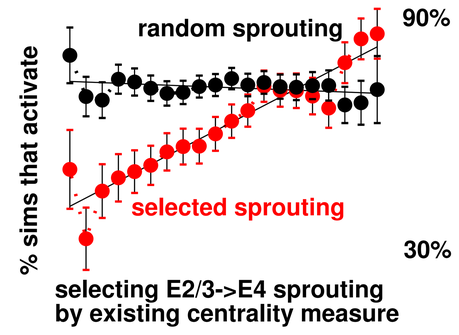
To look at multiple factors, we ask how well activation/not predicts unusually high (red) or unusually low (blue) measures. Effect strength is given by circle diameter for different layers (x-axis) across different measures (y-axis). Internal E2/3 (E2-E2) convergence and multiple measures into E5 are important. (We excluded here the NORMAL group where almost all networks activated as shown in histogram above.)

Using 46,464,000 measures



Sprouting

We predicted that sprouting along pathways involving E2/3 would increase number of hubs and thereby promote network activation. Tested by either sprouting from randomly chosen cells (black) or from cells chosen for existing low centrality (red left) or existing high centrality (red right).



Conclusions

1. L2/3 excitatory cells provide a central hub enabling cortical activation.
2. Reciprocal excitatory feedback between L5 and L2/3 also critical.
3. Standard neurobiological measures of type-specific convergence and divergence are more useful than general graph-theoretic measures in predicting dynamics.
4. Small variation in degree distribution in critical cell populations (layers) produces large changes in dynamics.

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Acknowledgments: Simulations performed in NEURON. Thanks to Mike Hines and Ted Carnevale for continuing assistance. Analysis performed in NEURON using NQS. Research supported by NIH (NS045612).