

Network Topology and Hippocampal CA3 Synaptic Connectivity

Gabriele Scheler `scheler@stanford.edu`

Center for Cognition and Neuroscience *Department of Computer Science*
Mountain View, Ca. 94040 *Stanford University*

Genetic Modifications of Synaptic Connectivity

In the hippocampal CA3 brain area, different types of genetic alteration lead to changes in synaptic connectivity. Ts65Dn (Down syndrome) mice have reduced input connectivity from the dentate gyrus (DG) area, and increased recurrent (CA3 \rightarrow CA3) connectivity, while fragile-X mosaic mice show reduced output connectivity for affected neurons, and dominance of synaptic connectivity by wild-type neurons. In both cases, the weight distribution for the connections is essentially unaltered ([1],[2]).

Constructing Graph Models

We constructed network models with topologies matching normal, Ts65Dn and fragile-X mosaic mice. For the normal model we used a regular, random, or a neighborhood structure (where the probability of a direct link between nodes is proportional to their distance), and then applied methods of graph alteration for Ts65Dn (increasing recurrent connections by 50%) and fragile-X mosaic structure (increasing connectivity by 100% for 20% of nodes, reducing connectivity by 10% for 80% of nodes). The results are summarized in Fig. 1. We see that the impact of the genetic modifications in synaptic connectivity depends on the underlying network topology: there is little effect on a random graph for fragile-X, but a regular graph or a neighborhood graph show alterations in path length and clustering. This is consistent with the idea of a less ordered connectivity associated with a fragile-X mosaic network structure. Secondly, the increased density of the Ts65Dn modification has opposite effects on a random graph vs. a graph with pronounced neighborhood structure. It reduces cluster index and mean path length, but increases the open cycle ratio (a measure of cyclicity) only for graphs with local structuring. This shows the co-existence of increased disorder and increased feedback loops for the Ts65Dn graph, consistent with a view of a more serious, but related abnormality in hippocampal processing. These implications of network topology impose mathematical constraints on neural computation independent of a particular neuronal processing model.

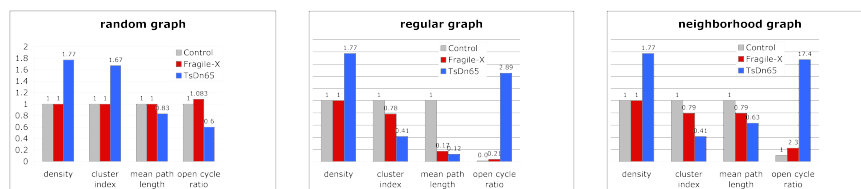


Figure 1: Modification of key network parameters by Fragile-X and TsDn65 for different topologies: the fragile-X modification reduces mean path length and cluster index for the regular graph, and its more realistic variant, the neighborhood graph, but has almost no effect on the random graph, the Ts65Dn modification increases the open cycle ratio, and reduces cluster index and mean path length for the regular and neighborhood graph, but has opposite or no effect on the random graph.

Applications to a Simplified Neural CA3 Circuit

We imported the neighborhood topology and its modifications into a neural circuit model of CA3 using a complex neural model for excitatory and inhibitory neurons and an exponential weight distribution ([3]). 10% of neurons were designed as inhibitory, and their connectivity was kept fixed. We stimulated the network models with continuous background input (to all neurons, $n=1000$) and localized input (to 50 selected neighboring neurons), and measured activity levels for all neurons in the network. Since dentate gyrus input is considerably less for the Ts65Dn model, we reduced stimulation to 50% in this model. The results are shown in Fig. 2. We see significant differences in spreading activation in response to focal stimulation for both types of genetic modification. The fragile-X modification shows more intermediate activation and less bounded activation, yet retains the stimulation focus clearly. The Ts65Dn graph shows pronounced activation spread and less contrast between the focus of stimulation and its environment.

Summary

How do graph topological results apply to processing in neural circuits? (1) There are genetic alterations in specific brain areas which affect the topology of the network. (2) Graph analysis reveals topological properties relevant for computation. (3) Creating neural circuit models with different topologies demonstrates an altered spreading activation response to focused stimulation which is independent of weight distribution and insensitive to fluctuations in

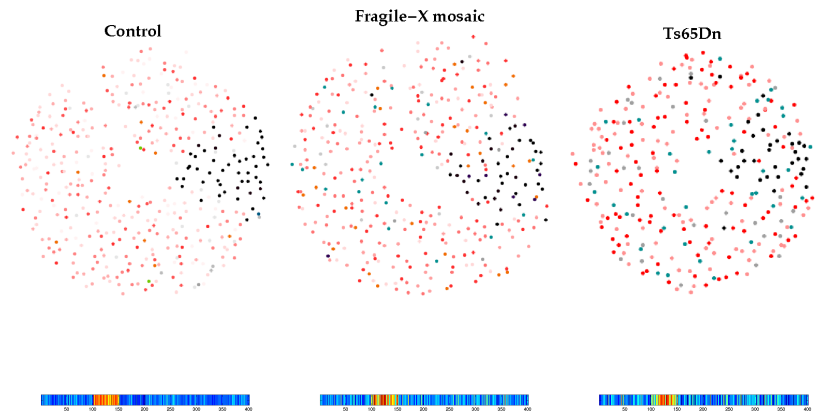


Figure 2: Activity levels in a network model of hippocampal area CA3 in response to localized stimulation. Excitatory hippocampal neurons (shown $n=400$) are laid out in a 1-D layer (below), and arranged as an energy-minimized graph (above, connections not shown). Stimulation was applied to 50 neurons. Activity is measured as spikes/neuron summed over 1000 ms.

input strength. The implication of the topological constraint for the processing of spatial information ('place' and 'grid' cells) will require further investigation.

References

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