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Effect of Genetic Heterogeneity on CA3 Network Architecture

William Hockeimer

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1 Opportunity

The hippocampus is a structure in the medial temporal lobe of the brain critically implicated in the storage of episodic memory and spatial navigation. It is currently though that the hippocampus' ability to encode information comes from its unique anatomical architecture. Diverse sensory input from cortical association areas impinges on the entorhinal cortex (EC), the main input the hippocampus, which in turn projects it to the first hippocampal subfield, the dentate gyrus (DG). According to the current theories, DG takes the highly correlated sensory information from EC and orthogonalizes it from other representation in a process termed pattern separation. This independent information is then sent to CA3, whose recurrent connections are thought to allow it it to retrieve stored information in a process called pattern completion. Given incomplete or degraded input from DG, CA3 can retrieve the full input therby instantiating a content addressible memory system. [1] There has been some recent experimental evidence suggesting the dual roles of DG/pattern separation and CA3/pattern completion is not without merit. [2].
Two aspects of network architecture are crucial to the computational abilities of CA3: 1) that it contains many recurrent fibers to perform pattern completion and 2) that it's activity patterns remain uncorrelated so that stored memory traces do not interfere with one another. Therefore classic theories of the content-addressable functions of CA3 have conceived of it as a fully-recurrent network with little thought (to my admittedly limited knowledge) of any further structure in the network architecture.

2 Challenge

This classic view of CA3 as a "generic" recurrent network may face some new challenges, however, thanks to the results of large scale gene expression analysis. A 2008 paper used data from the Allen Brain Institute to explore what genetic diversity, if any, exists within hippocampal CA3.[3]. The authors found a significant degree of heterogeneity in the expression of genes in CA3, notably genes involved in axon guidance. During development neurons follow complex chemical gradients of guidance cues, based on which cue receptors they express, which helps establish the connectivity pattern seen in the mature network. Given that there is a non-uniform pattern of axon guidance cue/receptor expression in CA3 and given that these molecules guide the formation of synapses, might the connectivity of CA3 be more complex than previously appreciated? What effect, if any, does the specific pattern of gene expression observed in CA3 have on its supposedly fully-recurrent architecture? And if there are differences what role might they have in supporting, or even hindering, the computational abilities of this key hippocampal subregion?

[1] Hopfield, John J. "Neural networks and physical systems with emergent collective computational abilities." Proceedings of the national academy of sciences 79.8 (1982): 2554-2558.

[2] Neunuebel, Joshua P., and James J. Knierim. "CA3 retrieves coherent representations from degraded input: direct evidence for CA3 pattern completion and dentate gyrus pattern separation." Neuron 81.2 (2014): 416-427.

[3] Thompson, Carol L., et al. "Genomic anatomy of the hippocampus." Neuron 60.6 (2008): 1010-1021.

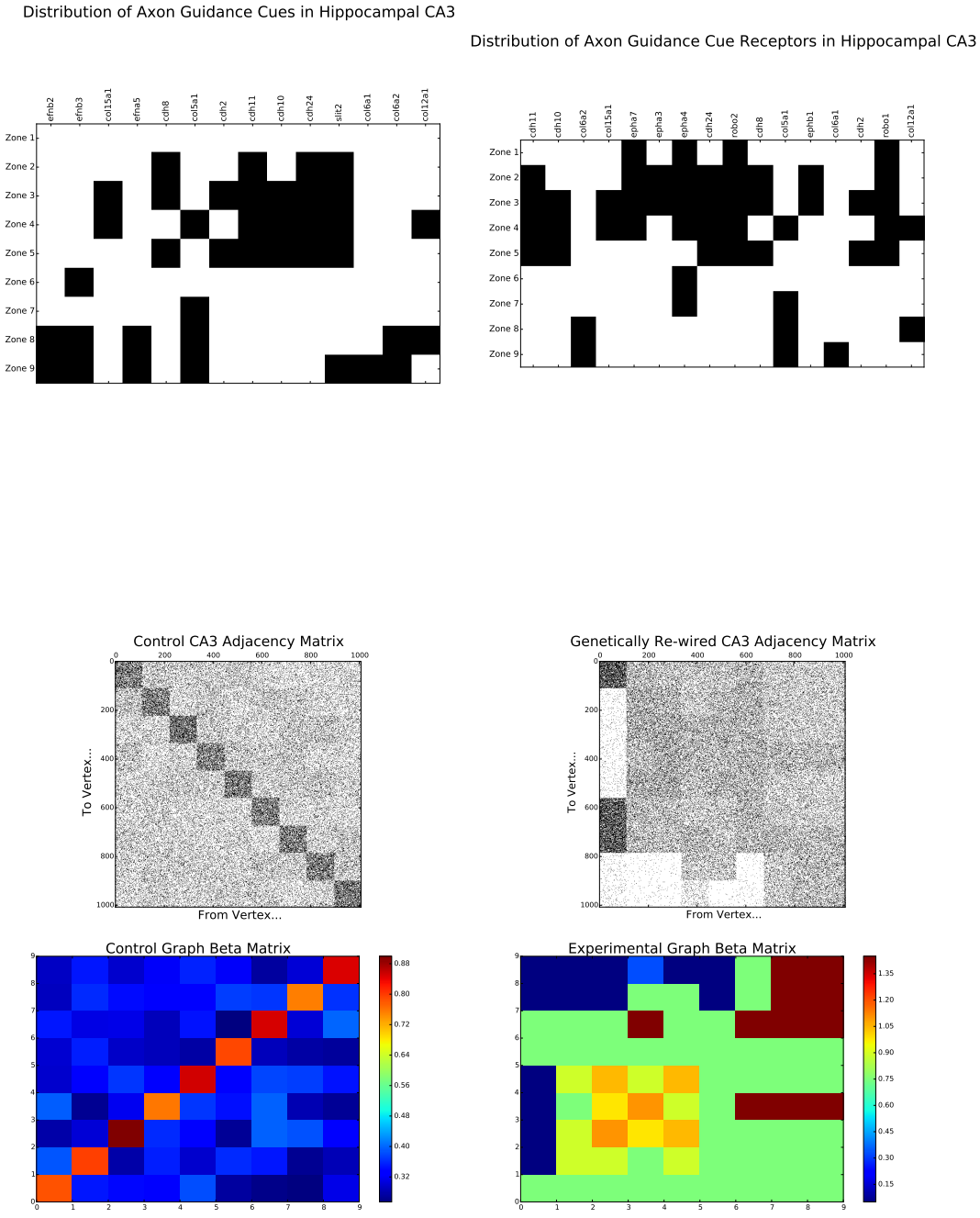
3 Action

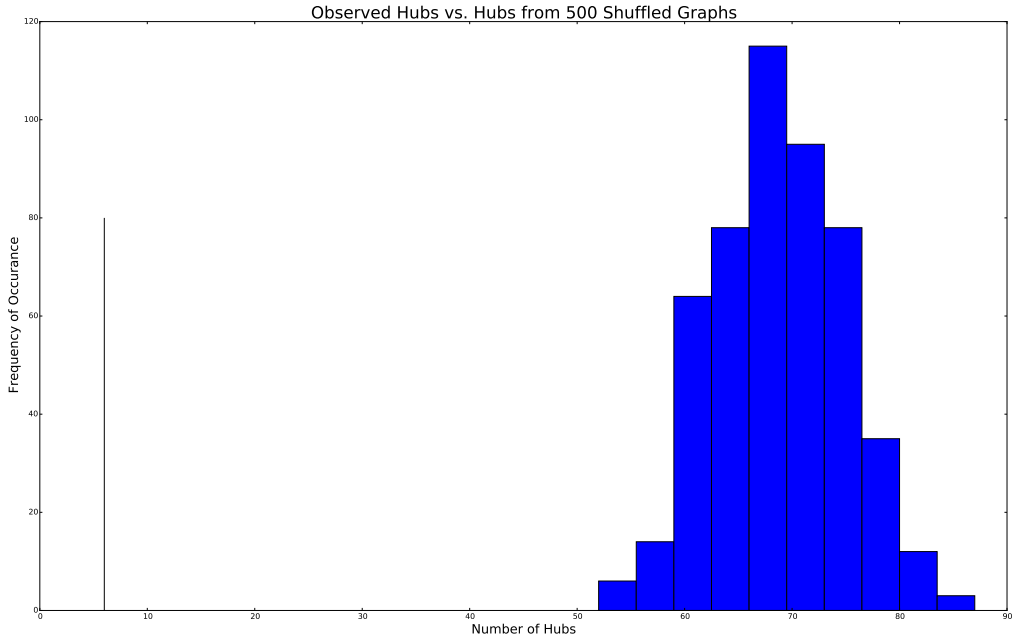
To explore the effect of genetic heterogeneity on CA3 network architecture I used the gene expression data from the paper to create a stochastic block model wherein each block was association with 2 bitstrings - one corresponding to the binary pattern of axon guidance cues in that region and another corresponding to the binary pattern of axon guidance cue receptors in that same region. Given known interactions between cues and receptors it was possible to create a rule book of they interact either attractively or repulsively. The ensemble interactions of all cues in region i and all cue receptors in region j allows a probability of connection from i to j to be computed and entered into the SBM beta matrix. This beta matrix was then used to probabilistically generate adjacency matrices, i.e. observed CA3 networks.

Figure 1 details the expression pattern of a select group of axon guidance cues and their receptors which are known to be especially important for driving axon targeting and also have well known interaction valences (i.e. attraction vs repulsion). Figure 2 shows two observed SBMS, one on the left from a control SBM and on the right from an experimental SBM that corresponds to a genetically rewired CA3. For the control network there were two different probabilities, one on-diagonal and one off-diagonal, which were randomly altered by a scaling factor. For the experimental model a score was computed for each i-to-j block interaction (i.e. the i,jth entry in the beta matrix) based on how the attractive vs repulsive cue balance normalized by how much attraction or repulsion would have been possible for that block given the number of cue/receptor hits present. Below each observed network is a beta matrix showing the probability distribution used to draw each SBM. Note the interesting structure to the experimental CA3 beta matrix.

Next I wanted to explore graph attributes of the CA3 network to see what effect, if any, the genetic rewiring had on the network architecture. I chose to look at hubs, defined as nodes receiving connections in excess of 1 SD of the mean. The rationale for exploring hubs is that I hypothesized that if the cue/receptor expression pattern had some effect on the network it would be in re-directing the flow of information through the network. Changing the pattern of connectivity from fully-recurrent (with no further structure) to something different (i.e. still recurrent but some further structure present) would possibly have an effect on the average density of connections and therefore the distribution of hubs. To analyze this I looked at the number of hubs present in an observed CA3 with a representative number of hubs (data on representativeness not shown) and ran a permutation test to see what the average number of expected hubs would be in a net with no structure. I also looked at the classic, fully recurrent net (data not shown). Fig 3 shows the distribution of hub frequencies from 500 permutations of the experimental adjacency matrix with a vertical line placed at the observed number of hubs. Clearly there is a stark difference in the number of hubs present. One interpretation of this is that the genetic patterning makes the network more homogeneous, paradoxically, than it would be without the heterogeneous genetic expression. CA3 is thought to perform pattern completion, or instantiate content-addressable memory, which requires the input patterns be decorrelated from one another. The presence of hubs in the network might hinder this goal by correlating different input patterns. The reason for this is that hubs, by definition, receive a large number of connections relative to other nodes and so integrate more information than do other nodes. Therefore they will be active

in more patterns than expected and will therefore correlate the patterns to the detriment of content-addressable memory retrieval.





4 Resolution

This pilot data shows us two things: first, what a genetically re-wired CA3 may look like and second, what graph features may be present in this network to aid in the computations being performed. Classic theoretical studies on CA3 have treated it as a generic recurrent network and so it is interesting to see what the network architecture looks like once empirical, genetic data is taken into account. Moreover, the graph theoretic analysis reveals some suggestive, albeit preliminary, data to suggest that this genetic patterning may make the network more homogeneous in its connectivity, thereby preserving the decorrelated input structure that a random or classically recurrent network might correlate to the detriment of memory storage and retrieval.

5 Future Work

The next steps are to further explore the graph attributes of the network such as betweenness, further measures of node centrality, and the presence of cycles. Then a functional assay will be used to explore what computational effects this genetic patterning actually has on pattern completion abilities. The classic and experimental networks will be converted into perceptron neural nets and trained on a pattern completion task. The performance of the networks on various metrics will be used to assess the functional implications of the genetic heterogeneity on CA3.