Effect of Genetic Heterogeneity on Content-Addressible Memory in CA3 EN.580.694 Final Project Proposal

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1 Opportunity

The mammalian hippocampus is a subcortical structure heavily implicated in processing both spatial and episodic information. The Cornu Ammonis 3 (CA3) region of the hippocampus is hypothesized to serve as a content-addressible memory system, crucial to the overall processing algorithm of the hippocampus, thanks to its extensive recurrent connections. In previous theoretical studies, CA3 has been conceived as a single, homogeneous network. Under this hypothesis, information is stored as patterns of neural activity. Given an incomplete portion of the input associated with a given pattern, CA3 is thought to retrieve the full, stored pattern. This process, known as pattern completion, is thought to rely on the recurrent connectivty of CA3. A landmark theoretical study showed that a generic recurrent network can in fact perform this type of task [1]. Recent experimental evidence suggests that CA3 does, in fact, perform pattern completion [2]. However, recent genetic evidence shows the existence of at least nine distinct genetic expression regions of CA3 [3]. This calls into questions whether or not the connectivity of CA3 is truly homogeneous and what effects, if any, this would have on the pattern completion abilities of CA3.

2 Challenge

The neuroscience community faces a challenge concerning how to best integrate this new genetic information and assess what effect, if any, this higher- resolution picture of CA3 affects the predictions made by modeling studies concerning

[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.

content-addressible memory. It remains to be seen, for example, if this genetic heterogeneity causes differential connectivity (compared to a fully-recurren network). If there is a deleterious effect work is needed to determine how CA3 evolved to overcome this limitation and if the effect is postive it warrants exploring how this unique connectivity confers some computational advantage.

3 Action

We will develop an Erdos-Reyni mixture model to explore how the presence of distinct genetic expression zones affects the connectivity, and therefore function, of CA3. The CA3 network will be represented as an Erdos-Reyni mixture model where each component of the model, ER_i corresponds to an empirically determined zone of unique genetic expression patterns. Each block of the model will be associated with a certain node attribute, a K-bit bitstring. Each bit of the string corresponds to a given gene and the value whether it's expressed (1) or not (0). We will use empirical studies to determine n candidate genes to include in the K-bit bitsring with inclusion reserved for those select genes which have been shown to play critical roles in establishing connectivity during development, such as the diffusible cue *Netrin* or the cue receptor *Unc*. A dictionary of rules will be created to determine how the different bits interact with one another. For instance, if one bit corresponds to *Netrin* and another corresponds to *Unc* then the rule for the associated nodes is that a node expressing each (i.e. has a "1" in the column associated with each) will have a higher likelihood of connectivity. The magnitude of this likelihood is a parameter than can be experimentally tuned. There will exist two Erdos-Reyni models: 1) under the null hypothesis the model (ER_1) will correspond to the classical, fully-recurrent model of CA3 familiar to the computational literature 2) an Erdos-Reyni mixture model (ER_9) with one component corresponding to each of the 9 genetically distinct subregions of CA3. Within each block of ER_9 will be n neurons, i.e. neurons are equally distributed within each block and there will be 3,000 neurons (1 percent of the total number). Each network will be used to define a 1-layer neural network which will subsequently be trained on a pattern completion task. The performance of each network can be assessed along multiple dimensions, including 1) maximum number of patterns that can be stored 2) maximum overlap between stored patterns 3) speed at pattern completion 4) minimum size of input pattern needed to retrieve whole pattern. The performance of each network on some given set of pattern completion tasks, for example some of those just mentioned, will be the outpuit used to judge how changing the connectivity

4 Resolution

We will run each network - ther ER_1 and ER_9 network on a pattern completion and assess how each network performs. This will help us understand how

the connectivity within a recurrent network affects its computational abilities and, specifically, how geneic subdomains of CA3 affect its ability to peform the pattern completion tasks so commonly associated with it.

5 Future

Future experiments will determine 1) the parameters of the pattern needed to achieve successful completion, 2) the degree of reconnection between sub- regions of CA3 that still allows a basal level of pattern completion to take place.

6 Statistic Decision Theoretic

6.1 Sample Space

G(V,E,Y) for ER_9 where V = 3,000 neurons E = $(0,1)^{vxv}$ and Y = 9 K-bit bitstrings (1 per block of ER model). G=(V,E) for ER_1, i.e. there are no bitstrings.

6.2 Model

$\text{SBM}_9^N(\rho, \beta) : \rho = \Delta_9, \beta \in (0,1)^{9x9}$

6.3 Action Space

A = $(0,1)^{nx1}$ where n is number of neurons, i.e., 3,000. In English, this is the output pattern of the pattern completion task.

6.4 Decision Rule Class

f $\longrightarrow G_p x A_p$ where subscript p indicates the graph activation and output pattern associated with input pattern p. f indicates whether G is a successful representation of A, i.e. whether the pattern successfully retreives p.

6.5 Loss Function

The MSE of the retrieved pattern from the null hypothesis network (ER_1) and the test network (ER_9) is computed across n patterns.

$$\text{L} = \text{MSE} = \frac{1}{n} * \sum_{k=1}^{n} (y_i - \hat{y})^2$$

6.6 Risk Function

R = E[L]