CS8803 - TOI Final Project: A Non-Invasive Statistical Test Based on Graph Theory for Detection of Early Stage Alzheimer's Disease

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1   Introduction/Motivation

For at least a decade, we have known that the brain is complex structural network, often referred to as a connectome [15, 22]. Moreover, the study of quantifying the brain's structural and functional systems using graph theoretical approaches to analyze the complex networks has been widely studied [1, 7, 17, 5, 2]. More specifically, graph theoretical analysis has been applied to quantifying neurological and psychiatric disorders in clinical and translational aspects as these disorders can be described as disconnectivity syndromes [19]. In particular, several experiments demonstrate empirical evidence from fMRI, EEG, or structural MRI brain data of patients with Alzheimer's Disease (AD) as having altered small-world network properties, neuronal path length, and increased global clustering compared to healthy brains [21, 19, 9, 20, 1]. Therefore, a possible way of identifying the evolution of and diagnosing AD could be through analyzing the change of the graph neuromarkers within the brain's connectome [6]. This comes in contrast to the popular hypothesis that overreliance on the amyloid/tau hypothesis for explaining AD's neurodegeneration, which has been criticized as having hindered diagnosis and cure discovery of AD [18].

In this work, we propose a statistical test for identifying early-stage AD based on graph properties of a sampled brain, which we will call G, with theoretical guarantees of accuracy and computational complexity. Previous work on analyzing the correlation between certain graph properties of EEG and MEG data of brains with AD have primarily focused on the correlation of path length and clustering coefficient against AD neurodegeneration [3, 24]. Although empirical evidence for a strong correlation between the small world (SW) graph property is less rigid [11, 8], [23] has demonstrated that analyzing a brain's small world properties in conjunction with other neuronal features for diagnosing mild cognitive impairment (MCI) patients with AD with high accuracy.

Therefore, assuming we have a sampled brain connectome from a patient G, constructed from EEG or MEG data, we hypothesize that if the sampled graph deviates too far from the SW assumption we can classify the brain as having AD. The definition of the SW assumption we use is that nodes close to each other in physical space are more likely to connect compared to nodes that are farther away. One of the most popular random graph models for modeling the SW assumption is the Watts-Strogatz model, which aims to generate a graph with average shortest path length and large global clustering coefficients [25]. The problem with this model is that the Watts-Strogatz model has been criticized as not modeling realistic networks that are often scale-free networks inhomogenous in degree and imply a fixed number of nodes. A scale-free network is defined as a network whose degree distribution follows a power law, which means that the fraction $P(k)$ of nodes in the network having k connections to other nodes goes like $P(k) \sim k^{-\gamma}$ for large values of k and where typically $2 < \gamma < 3$ [12].

2 Definitions/Preliminaries

Instead of using the Watts-Strogatz model to model the SW assumption, we model the assumption using a soft random geometric graph (RGG). We assume that the sampled graph G is either an Erdős-Renyi random graph, a random graph without the SW assumption, or a soft RGG, one with the SW assumption. We will specifically examine a d-dim Gaussian RGG. A d-**dim Gaussian RGG** is defined as a graph $G = G_\sigma = (V, E)$, with $V = \{v_1, v_2, \ldots, v_n\}$ where each vertex is randomly chosen at random from $[0, L]^d$. Then an edge between vertex x and y is present in the graph with probability[16]:

$$\mathbb{P}(\mathbb{1}_{(x,y)}) = g(x, y) = e^{-\frac{\|x-y\|_2^2}{2\sigma^2}}$$

Without loss of generality, we can consider that $L = 1$, so the nodes are distributed in a unit cube and, that $d = 3$, which represents the dimensions of physical space.

If we can prove with high probability that the sampled graph G is not a soft d-dim Gaussian RGG, then one cannot guarantee the claims of the k-cap process presented in [16]. Specifically, one cannot guarantee that the k-cap process on the graph, after some time t, will be covered by a single ball. In the context of the brain, the intuition is that neuronal signals will have difficulty converging into centralized neuronal hubs if the graph's connections do not obey the main assumption of a soft RGG: the probability an edge $\mathbb{1}(x, y)$ exists between two vertices is a function of the hidden variables of the endpoints, which we equate to the SW assumption. In this case, the hidden variables of the endpoints are the relative physical coordinates of two neurons. Additionally, the lack of convergence of neuronal signals to a centralized hub mirrors symptoms of AD.

Another definition we use is that of a **hard RGG** which is distributing the vertices in a space $[0, 1]^d$ identical to the soft RGG but an edge exists from vertex x to vertex y iff $\|x - y\|_2 \leq r$. Sometimes r is parametrized by a probability p such that the probability between any two edges is p, making it identical to an Erdős-Renyi random graph $G_{n,p}$. Notice that the soft RGG is a generalization of the hard RGG we can think of the hard RGG as having an edge probability of 1 up to a certain radius r and falling to 0 at any distance farther. The soft RGG model has more flexibility because we can have the edge probability function be approximately 1 up to a radius and then drop off exponentially, not sharply, after it passes that radius. An extension of the hard RGG model proposed by [10] is the directed RGG model, which has the radius of each vertex as a unique random variable. It has been proven to be scale-free for indegree distribution, has binomial outdegree distribution, has a high clustering coefficient, and has few edges, which makes it likely to be small-world. Since the soft RGG model is a generalization of the hard RGG model, this means that potentially we could represent the Directed RGG model as a soft RGG model for a specific edge probability function parametrized by a random variable.

3 Setup

Suppose we are given a graph that is either drawn from an Erdős-Renyi random graph $G_{n,p}$ or generated by the 3-dim Gaussian RGG algorithm $G_{n,\sigma}$. Here p and σ are chosen such that the expected total number of edges is the same for both $G_{n,p}$ and $G_{n,\sigma}$. This is a valid assumption for the test because the logic is similar to MLE estimation: given data that has the real value X, assume parameters are the ones of highest probability when fitting a model to the data X. We choose n to be sufficiently large such that $d = 3 < \log^3 n$, which means that $n >> e^{3\sqrt{3}}$ because [4] has proven that any smaller values of n will lead the expected clique numbers of an Erdős-Renyi random graph $G_{n,p}$ and a hard RGG behave quite similarly, which means that they will be hard to distinguish. Since we are planning on analyzing the graph properties of the expected maximum degree Δ_k, where $n = k^\beta$ for some $\beta \geq 5$ and $\sigma = O(k^{-1/3})$. Since σ needs to be defined such that the expected total number of edges is the same for both and it relies on k, and k depends on β, we essentially assume a β such that σ creates a geometric random graph equivalent to a $G_{(n,p)}$ model. For an Erdős-Renyi random graph $G_{n,p}$, it is known with high probability, the expected maximum degree for $G_{(n,p)}$ is:

$$E[max_{v \in V} deg(v)] = np + O(\sqrt{np \log n})$$

Moreover, for a hard RGG let (r_n) be a sequence of radii such that as $n \to \infty$ then $\frac{\log(\frac{1}{nr_n^3})}{\log(n)} \to 0$ and $\frac{nr_n^3}{\log n} \to 0$ One can verify these assumptions are correct by empirically collecting evidence from the graph G as n varies and constructing (r_n) in such a way that they hold. Moreover, these are reasonable assumptions to hold because they imply that X_n tends to ∞ as $n \to \infty$ but not too fast.

Now, let:

$$X_n = \frac{\log n}{\log \frac{\log n}{nr_n^3}}$$

Then the following are true as proven by [13]:

$$\lim_{n \to \infty} \frac{\Delta_k}{X_n} = 1 \text{ with high probability}$$

[13] did not provide any guarantees on the rate of convergence, but we can approximate the $\Delta_k \approx X_n$ for an arbitrarily large n. However, the approximation will always be a slight underestimation.

Finally, we defined the dimensionality of neurons to be $d = 3$, and they are uniformly random distributed in the unit cube $\{0, 1\}^3 \in \mathbb{R}^3$.

4 The Statistical Test

We will provide a test by analyzing the expected maximum degree Δ_k. Choose a vertex randomly and then also get the k closest vertices from V and call this set A_0. Construct a new graph such that if $a_0, a_1 \in A_0$ and $r := \frac{1}{2}\sigma\sqrt{\log \log k}$ all vertices in A_0 such that $\|a_0 - a_1\|_2 \le r$ are connected by an edge. Then we can use the results from [13] because we have a definition for r. Notice that since we are in the unit cube $\|a_0 - a\|_1 \le \sqrt{3}$ for all v which implies that $0 \le r \le \sqrt{3}$ (and in general $\sqrt{3}L$ for cubes of length L). We call this newly constructed graph G_0. We choose this r because by Lemma 9 from [16], the maximum degree of this graph should be, with high probability, X_n.

Then we define v_k as the node with the highest degree in G_0 (if there are ties we randomly choose a vertex). Let $\Delta_k = \sum_{v \in V, v \neq v_k} Y_{v_k v}$ where $Y_{v_k v} = 1$ if v_k has an edge to v. For G_0, the expected value of the number of neurons within this newly created graph is the proportion of the volume of the sphere generated by r to the volume of the unit cube since the neurons are uniformly distributed. For example, in 2-Dimensions:
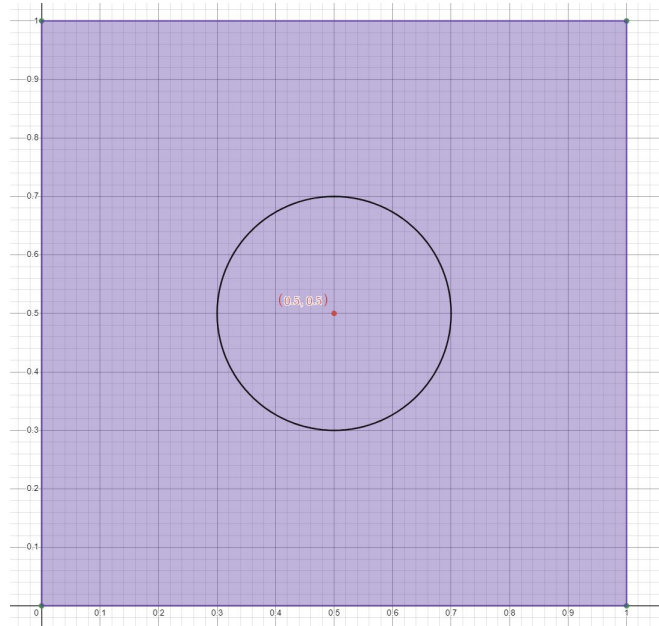
Therefore, the number of neurons is expected to be $n_0 = \frac{\frac{4}{3}\pi r^3}{1} * n = \frac{4}{3}\pi r^3 n$, which means that the expected maximum degree if p is constant would be $n_0 p + C\sqrt{n_0 p \log n_0}$ for a sufficiently large C.

Notice that, if p is constant, then $deg(v_k)$ is a binomial random variable with mean $n_0 p$. Therefore, we can use the Chernoff bound:

$$Pr(deg(v_k) > n_0 p + C\sqrt{n_0 p \log n_0})$$

$$= Pr(deg(v_k) > n_0 p + C n_0 p \frac{\sqrt{\log n_0}}{\sqrt{n_0 p}})$$

$$= Pr(deg(v_k) > n_0 p(1 + C\sqrt{\frac{\log n_0}{n_0 p}}))$$

$$\leq \exp\left(-\frac{C^2 \frac{\log n_0}{n_0 p} * n_0 p}{2 + C\sqrt{\frac{\log n_0}{n_0 p}}}\right)$$

$$= \exp\left(-\frac{C^2 \log n_0}{C\sqrt{\frac{\log n_0}{n_0 p}}}\right) = \exp\left(-\frac{C\sqrt{\log n_0}}{\sqrt{\frac{1}{n_0 p}}}\right) = \exp(-C\sqrt{n_0 p \log n_0})$$

$$\leq \exp(-C\sqrt{\log n_0})$$

We note that as $n_0 \to \infty$ the probability goes to 0, so we can control this probability by adjusting n_0. Since n_0 is positively correlated with n, i.e. $n_0 \propto n$, this means increasing n will increase the accuracy of this test. Therefore if v_k's degree exceeds $n_0 p + C\sqrt{n_0 p \log n_0}$ we classify it as a random geometric graph, i.e. that it abides by a small world assumption. Otherwise, we classify it as $G_{(n,p)}$ which does not follow a small-world assumption. The accuracy of this classification depends on n and thus if we set n arbitrarily large we can achieve a constant accuracy. Notice that even though we only tested a subset of vertices, the random geometric graph's main assumption is a local property that should apply to any vertex.

In terms of runtime, in the first step, we sample k vertices from the graph G, which is bounded by $O(n)$. Calculating pairwise distances between vertices takes at most $O(n)$ time, though it could be reduced to O(n) since the distance values are symmetric. Finding the node with the highest degree in G_0 would take $O(n^2)$ time, Therefore, the runtime would be around $O(n^2)$. This excludes parameter estimation of β, which enables the total number of edges of both $G_{(n,p)}$ and $G_{(n,\sigma)}$ to be identical. Moreover, in terms of sample size/complexity, it makes no guarantees on how fast the accuracy will converge since n is the only tunable parameter and we can only guarantee it is positively correlated with n_0.

Intuitively, this statistical test attempts to exploit the spatial placement of the neurons/vertices to distinguish the different graph models. We define the null hypothesis $H_0 = G_{(n,p)} \to$ no small world assumption $\to$ signs of AD. By choosing a radius r, and therefore an expected n_0, we examine a certain radius where we have known claims from [16] about the expected maximum degree Δ_k in this radius. Also, it mirrors a similar proof method from [16] in the concept of initializing A_0. In the context of neuroscience, this test assumes that the brain network is healthy and obeys the small world assumption/can be modeled by a 3-dim Gaussian RGG. Therefore, if we pick a certain subset k of the vertices and consider them to be the initial firing, assuming the assumptions of this graph from [16], then it should converge to a spatial area bounded by a ball defined in [16] simply by the degree connections made by the small world assumption. Otherwise, if we sample some subset k, and the Δ_k of v_k is in the expected region for a $G_{n,p}$ model, then likely it does not follow the small world assumption. It might be necessary to sample all $\frac{n}{k}$ subsets of vertices of G to reduce the error of the test since the small world assumption is not guaranteed everywhere in the brain.

5   Simulation Discussion

We performed some simulations to help visualize the test in the Appendix: Section 7. We essentially approximate a brain's connectome as a random graph with neurons distributed uniformly at random in the unit square. We choose parameters that enable our assumptions to be true and then compare the graphs generated if we were to use a soft RGGs edge probability function and a $G_{(n,p)}$'s edge probability function. First, we experiment with how parametrizing σ affects the edge probability function. Notice that σ essentially acts as a soft radius if we were to equate it to the definition of a hard RGG. As σ increases, the probability of more distantly connected vertices/neurons increases as shown in 1. Next, holding the neuron's positions constant, we construct two different random graphs based on the different models for the edge probability function 2 3. Something interesting to note is that although the total number of edges between the two graph models is approximately the same, one can see that the distribution of the edges in the $G_{n,\sigma}$ 2 is more concentrated around areas where the nodes are close. There are regions of space between the neurons where no edge ever crosses. However, in 3, one can see that the edges generally cover all of the space and do not concentrate around vertices. The contrast between these two graphs demonstrates that one could potentially distinguish the two graph models by how the edges are distributed which gives evidence to support the assumption that the $G_{n,\sigma}$ is a good model for the SW assumption and that, more importantly, $G_{n,p}$ does not.

Now, we examine what happens when we randomly sample a vertex and get the k closest vertices. Comparing 4 with 5, it becomes clear that if we look at the k closest vertices, there are more edges in the $G_{n,\sigma}$ model than the $G_{n,p}$ model. Although based on the distance matrix 1 the vertices are greater than the threshold of $r = \frac{1}{2}\sigma\sqrt{\ln \ln k} \approx 0.0286$, since they are of the same order of magnitude we can assume that all the edges in 2 are included in the construction of G_0. By the definition of X_n we expect it to be around $\frac{\log 5}{\log \frac{\log 5}{5(0.0286)^3}} = 1.045$.

Also, for $G_{n,p}$ the maximum degree is around $5(0.054) + C\sqrt{5(0.054)\log 5} \approx 0.27 + 0.43C$ for some C. These are ***extremely rough*** approximations, but still, there seems to be some difference between the two values, which merits using the property examined in the test. Furthermore, the relationships are supported by 2, because the Soft RGG degree's maximum degree of 4 is much larger than the max ER degree of 1. Therefore, we expect the value of the maximum degree in a graph without the SW assumption to be significantly smaller when we construct G_0.

6   Limitations/Future Work

Obviously, this test is not meant to be immediately implemented in clinical applications due to certain assumptions we have made. However, it could serve as a theoretical basis for an actual test that screens for AD by testing the SW assumption. Moreover, several other graph-theoretical symptoms of AD were not considered in this test, which means that this test should only be used in conjunction with other modes of diagnosis to further support a decision. Additionally, empirical evidence demonstrates that the SW assumption does not hold everywhere in the brain. On the other hand, this test does provide theoretical bounds on the accuracy of the test, which could mirror real relations of the number of nodes/neurons n in the accuracy of an actual test. Perhaps certain assumptions of the test can be improved/modified when attempting to apply this test to actual brain network reconstructions from fMRI/EEG data. A possible future work is to use the test to distinguish $G_{n,p}$ from the Directed RGG proposed in [10] because they proved various properties of the graph related to the SW assumption, so that graph might better model the SW assumption. This might not take a significant amount of work because potentially one can parametrize the edge probability function $g(x)$, specifically σ, as a unique random variable for each vertex to make the model equivalent to the Directed RGG. This is because the Directed RGG is hard, but the radius is a random variable for each vertex. By potentially combining aspects of both $G_{n,\sigma}$ and the Directed RGG, one could find a more generalized model that employs the SW assumption which would enable one to use fewer assumptions to guarantee some of the claims proven in [10, 16, 14]. In turn, that could potentially lead to a more precise/realistic test for diagnosing AD based on graph theory.

7 Appendix: Simulations

We analyze when $d = 2$ for the sake of visualization. Based on [16], in their definition of the d-dim Gaussian soft RGG, all vertices in the graph can be considered. In $d = 2$, when points are randomly generated in the unit cube, the maximum distance between two points is $\sqrt{2}$, when the two points are at the opposite corners of the cube. Therefore the edge probability function can be simplified to:

$$g(x) = e^{-\frac{\|x\|^2}{2\sigma^2}}$$

For a specific vertices v, iterate through all other vertices and calculate v's distance to that vertex x. Then the probability that the vertex is connected to that vertex is defined by $g(x)$. In this plot, we analyze how σ affects $g(x)$ and σ is essentially what is used to tune the radius as used in the definition from [14].
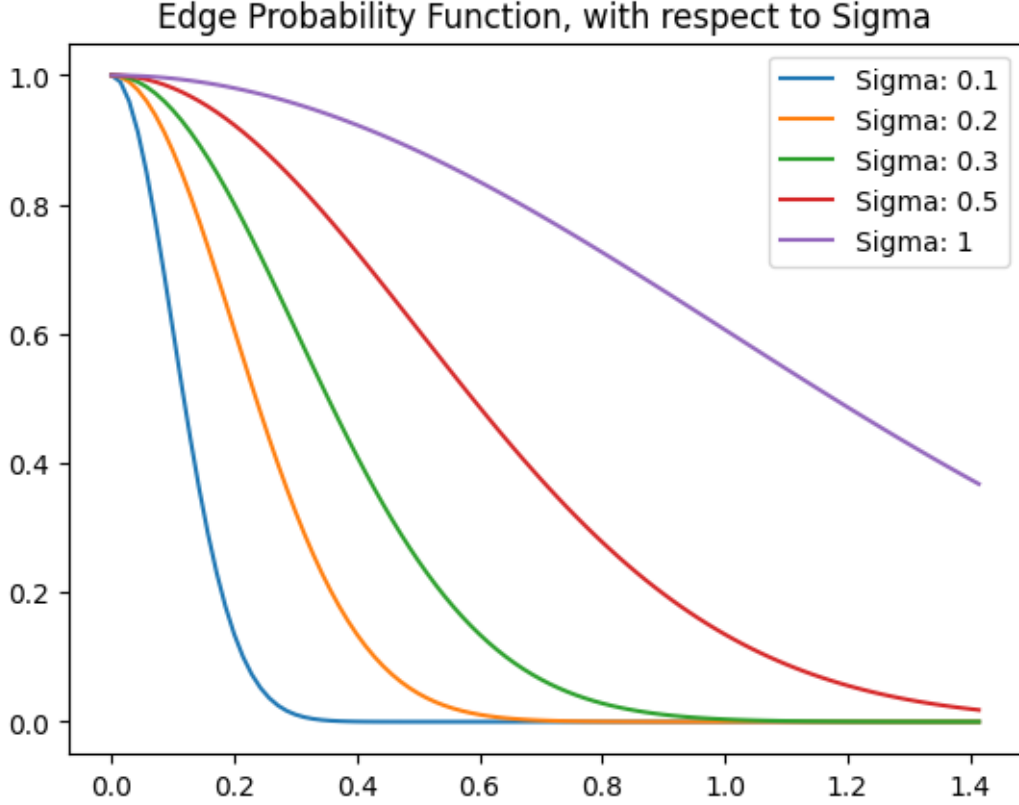

Figure 1: X axis is distance, Y axis is Probability

Then, create a hypothetical randomly generated graph using NetworkX with $n = 500$ neurons/vertices. Since $d = 2$, n is approximately arbitrarily large such that it is easy to distinguish between $G_{(n,p)}$ and $G_{(n,\sigma)}$. We arbitrarily set $\beta = 5$ such that $k \approx 3.465724$ and we let $\sigma = \frac{5}{\sqrt{k}}$, which makes $\sigma \approx 0.1002$. To ensure that the number of total edges is equal to $G_{(n,p)}$ note that this value is $\binom{n}{2}p$. So, we first numerically approximate the total number of edges of a random geometric graph using these parameters by sampling 100 soft 2-dim Gaussian Soft RGGs and taking the average of the total number of edges, which comes out to be 6740.44. Letting:

$$\binom{n}{2}p = \frac{n(n-1)}{2} \times p = 6740.44$$

we get that $p \approx 0.054031$. Running numerical simulations for generating a $G_{(n,p)}$ using these parameters as the average over 100 sampled graphs is 6746.46. The neurons were randomly uniformly generated in the unit square with a fixed seed that is the same for each iteration of these simulations. Plotting these random graphs using the same seed used to generate the neurons, we get:
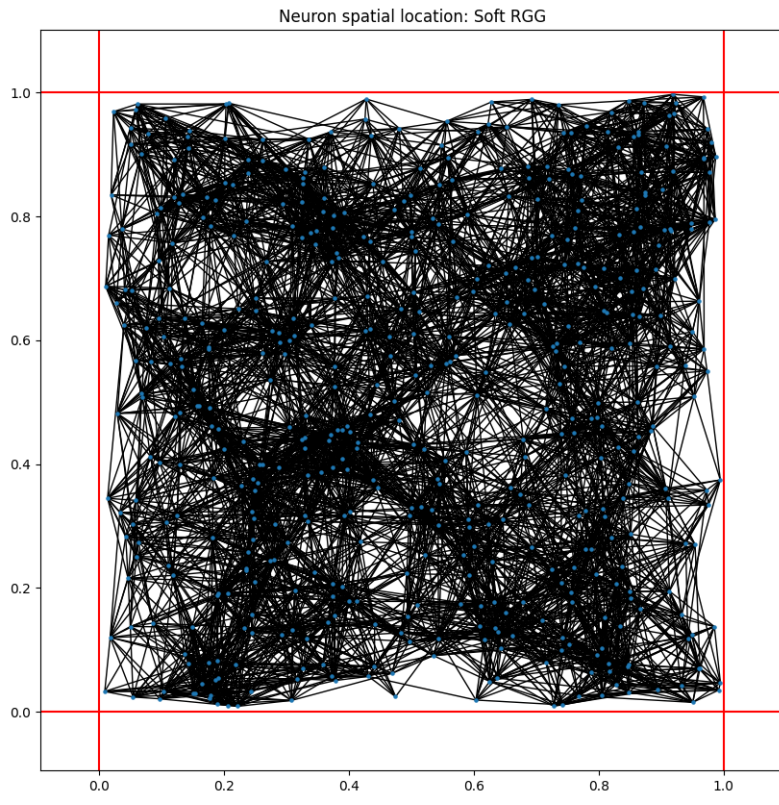
6

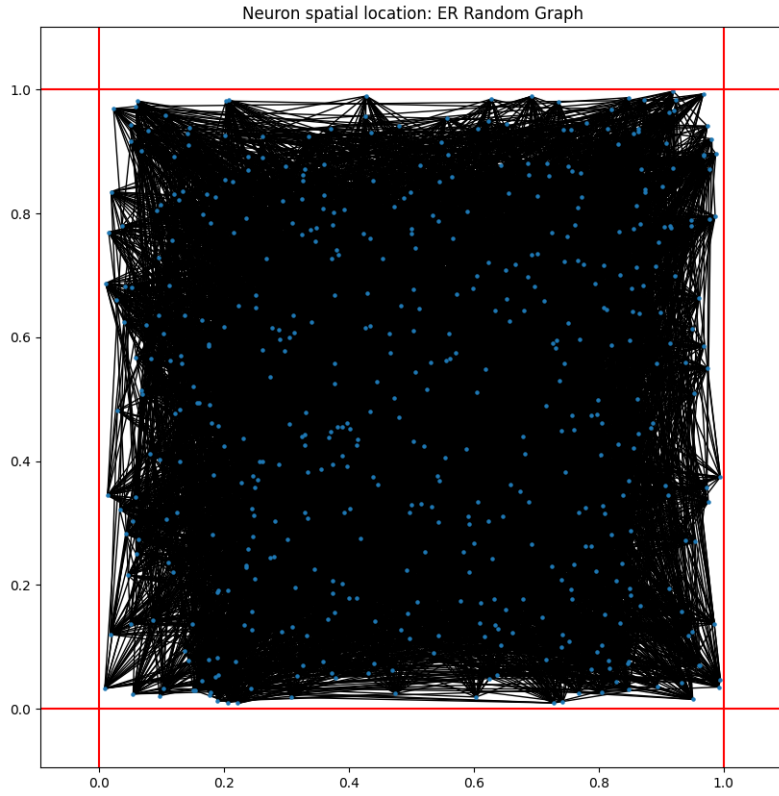Figure 2: Soft 2-dim Gaussian RGG with $\sigma = 0.1002$

Figure 3: Erdős-Renyi random graph with $p = 0.054031$

In the soft RGG graph, there are 6651 edges and in the $G_{(n,p)}$ graph there are 6745 edges.

Next, let's analyze $k \approx 4$ with and consider the subset by sampling vertex indexed at 152 and get its 3 closest neighbors $[133, 443, 398, 71]$. Below are the subgraphs using only these 4 indices for both types of graphs:
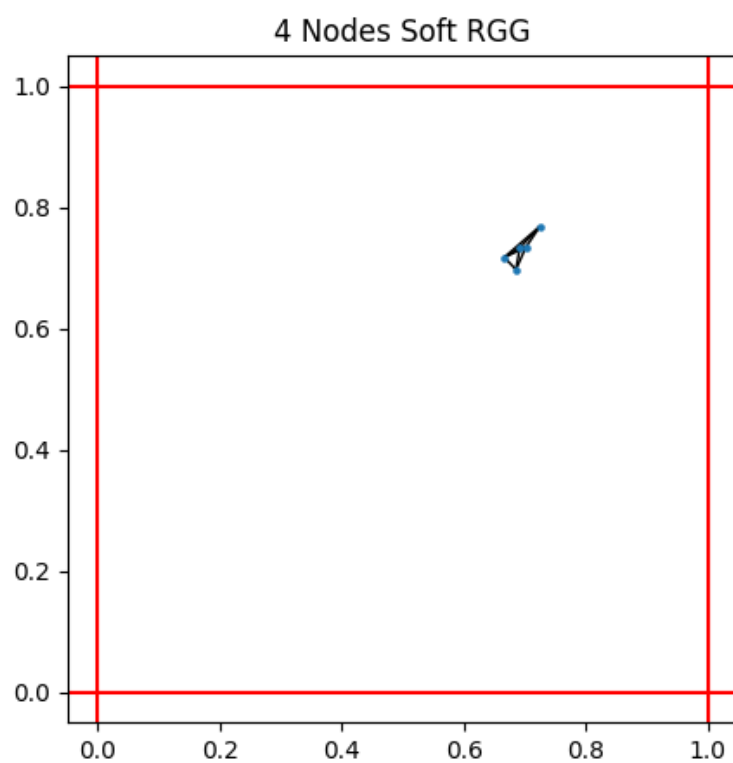
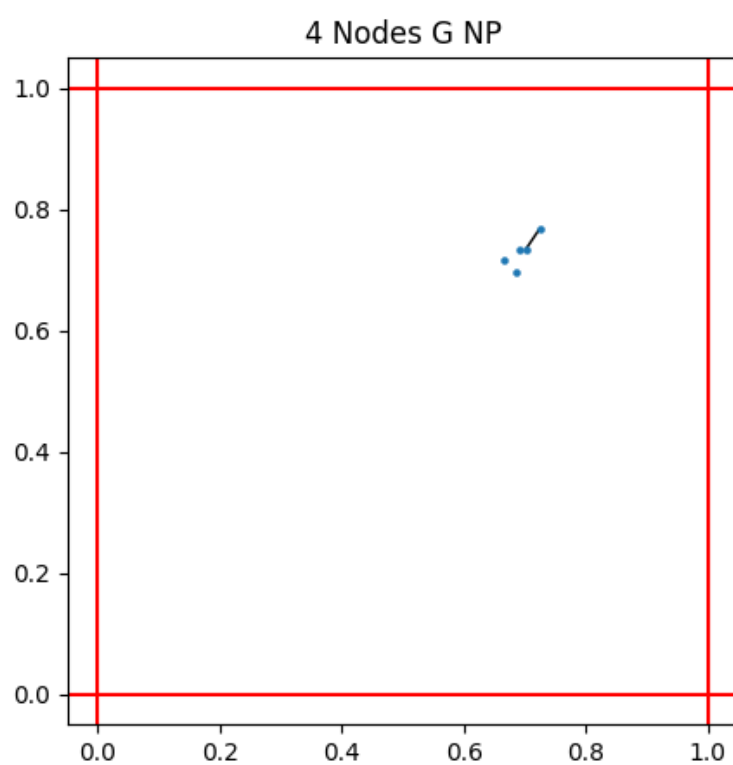Figure 4: Subgraph of 2 with nodes 133, 443, 398, 71, and 152

Figure 5: Subgraph of 3 with nodes 133, 443, 398, 71, and 152

8

The distance matrix is as follows:

Node Index	133	443	398	152	71
133	0	0.029874	0.036487	0.00990387	0.04805
443	0.029874	0	0.02766	0.0389128	0.07731
398	0.036487	0.02766	0	0.04008	0.081
152	0.00990387	0.0389128	0.04008	0	0.0413
71	0.04805	0.07731	0.081	0.0413	0

Table 1: Euclidean Distance Matrix of nodes 133, 443, 398, 71, and 152

The degree table is as follows:

Node Index	Soft RGG Degree	ER Degree
133	4	0
71	3	1
398	3	0
152	4	1
443	4	0

Table 2: Degree of nodes 133, 443, 398, 71, and 152 in 4 and 5

All the code used to generate these images can be found on:
https://github.com/MatthewChen37/CS8803TOI-Simulations/blob/main/Simulations.ipynb.

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