Quantum Edge Entropy for Alzheimer's Disease Analysis

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Abstract. In this paper, we explore how to the decompose the global statistical mechanical entropy of a network into components associated with its edges. Commencing from a statistical mechanical picture in which the normalised Laplacian matrix plays the role of Hamiltonian operator, thermodynamic entropy can be calculated from partition function associated with different energy level occupation distributions arising from Bose-Einstein statistics and Fermi-Dirac statistics. Using the spectral decomposition of the Laplacian, we show how to project the edge-entropy components so that the detailed distribution of entropy across the edges of a network can be achieved. We apply the resulting method to fMRI activation networks to evaluate the qualitative and quantitative characterisations. The entropic measurement turns out to be an effective tool to identify the differences in structure of Alzheimer's disease by selecting the most salient anatomical brain regions.

Keywords: Alzheimer's disease · Bose-Einstein statistics
Fermi-Dirac statistics · Network entropy

1 Introduction

Functional magnetic resonance imaging (fMRI) has provided a sophisticated means of studying the neuro-pathophysiology associated with Alzheimer's disease (AD) [11]. It maps the network representation to neuronal activity between the various brain regions. The resulting network structure has proved useful in understanding Alzheimer's disease (AD) via the analysis of intrinsic brain connectivity [10]. Although there is converging evidence about the identity of the affected regions in fMRI, it is not clear how this abnormality affects the functional organisation of the whole brain.

Analysis tools derived from measures of network entropy have been extensively used to characterise the salient features of the structure of network systems arising in biology, physics, and the social sciences [1–3]. In particular ideas from statistical mechanics and information theory have been used to develop techniques and analyse the time evolution of network structure using analogies with both classical and quantum systems. For example, the von Neumann entropy can be used as an effective characterization of network structure, commencing from

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a quantum analogue in which the Laplacian matrix plays the role of the density matrix [1]. Further development of this idea has shown the link between the von Neumann entropy and the degree statistics of pairs of nodes forming edges in a network [2], which can be efficiently computed for both directed and undirected graphs [3]. Since the eigenvalues of the density matrix reflect the energy states of a network, this approach is closely related to the heat bath analogy in statistical mechanics.

These promising approaches from statistical mechanics [4], thermodynamics [5] or quantum information [6] provide a convenient route to network characterisation. A well-explored study is an analogy of combining the networks with thermodynamic system [7]. The Hamiltonian operator identifies the energy states of a network by using the eigenvalues of a matrix characterisation. By mapping the network system occupied by a set of particles, the energy states are supported to be populated these particles in thermal equilibrium with the heat bath [7]. The occupation of particles in the energy states is populated according to the specific distribution. Specifically, these associated with the assumptions concerning the quantum spin statistics, namely Bose-Einstein and Fermi-Dirac statistics. From the relevant partition function, the thermodynamic entropy can be derived to characterise networks [7].

Although entropic network analysis using the heat bath analogy provides a useful global characterisation of network structure, they do not lend themselves to the analysis of the entropy of edge or subnetwork structure. In this paper, we explore a novel edge entropy projection which can be applied to the global network entropy computed from statistical mechanics using both the classical Boltzmann distribution and the quantum Bose-Einstein and Fermi-Dirac statistics [7]. The new characterisations of edge entropy resulting from this analysis allow us to probe in finer detail the interactions between different anatomical regions in fMRI data from healthy controls and Alzheimer's disease sufferers (AD).

It as been noted that AD subjects exhibit significantly lower regional connectivity and exhibit disrupted the global functional organisation when compared to healthy controls [8]. Because Bose-Einstein particles coalescence in low energy states and Fermi-Dirac particles have a greater tendency to occupy high energy states because of the Pauli exclusion principle, these types of spin statistics lead to very different distributions of entropy for a network with a given structure (i.e. a set of normalised Laplacian eigenvalues) [7]. Moreover, we wish to investigate them as a means of characterising differences in the network structure at low temperature. The analysis of the distribution of edge entropy within a network reveals that the different quantum statistics can be used to explore how the distribution of edge-entropy encodes the intrinsic differences in the anatomical pattern of fMRI responses between different groups having Alzheimer's disease and normal healthy controls.

This paper is organised as follows. Section 2 briefly reviews the basic concepts in network representation, especially with sophisticate study of von Neumann entropy. Section 3 reviews density matrix and Hamiltonian operator on graphs, and decompose the thermodynamic entropy on edges from Bose-Einstein and

Fermi-Dirac statistics. Section 4 provides our experimental evaluation. Finally, Sect. 5 provides the conclusion and direction for future work.

2 Graph Representation

In this section, we provide the basic background of graph representation and basic quantum theory. We briefly introduce the concept of the normalized Laplacian matrix as the density matrix in the definition of von Neumann entropy.

2.1 Preliminary

Let $G(V, E)$ be an undirected graph with node set V and edge set $E \subseteq V \times V$, and let V represent the total number of nodes on graph $G(V, E)$. The adjacency matrix of a graph is A with the degree of node u is $d_u = \sum_{v \in V} A_{uv}$. Then, the Laplacian matrix is $L = D - A$, where D denotes the degree diagonal matrix whose elements are given by $D(u, u) = d_u$ and zeros elsewhere. The normalized Laplacian matrix $\tilde{L}$ of the graph G is defined as $\tilde{L} = D^{-\frac{1}{2}} L D^{\frac{1}{2}}$, and the spectral decomposition is $\tilde{L} = \Phi \tilde{\Lambda} \Phi^T$, where $\tilde{\Lambda} = diag(\lambda_1, \lambda_2, \ldots \lambda_{|V|})$ is the diagonal matrix with the ordered eigenvalues as elements and $\Phi = (\varphi_1, \varphi_2, \ldots, \varphi_{|V|})$ is the matrix with the ordered eigenvectors as columns.

2.2 von Neumann Edge Entropy

The density matrix describes a system with an ensemble of pure quantum states $|\psi_i\rangle$ and each with probability p_i. It is defined as $\boldsymbol{\rho} = \sum_{i=1}^{V} p_i |\psi_i\rangle\langle\psi_i|$. The density matrix for a graph or network can be achieved by scaling the normalised Laplacian matrix by the reciprocal of the number of nodes [1,6]. It is defined as $\boldsymbol{\rho} = \frac{\tilde{L}}{V}$. This interpretation opens up the possibility of characterising a graph using the von Neumann entropy from quantum information theory. Therefore, the von Neumann entropy is given in terms of the eigenvalues λ_1, ..., $\lambda_{|V|}$ of the density matrix $\boldsymbol{\rho}$[1],

$$S_{VN} = -\mathrm{Tr}(\boldsymbol{\rho} \log \boldsymbol{\rho}) = -\sum_{i=1}^{|V|} \frac{\lambda_i}{|V|} \log \frac{\lambda_i}{|V|} \tag{1}$$

In fact, Han et al. [2] have shown how to approximate the calculation of von Neumann entropy in terms of simple degree statistics. Their approximation allows the cubic complexity of computing the von Neumann entropy to be reduced to one of quadratic complexity using simple edge degree statistics, i.e.

$$S_{VN} = 1 - \frac{1}{|V|} - \frac{1}{|V|^2} \sum_{(u,v) \in E} \frac{1}{d_u d_v} \tag{2}$$

Therefore, the edge entropy decomposition is given as

$$S_{VN}^{edge}(u, v) = \frac{1}{|E|} - \frac{1}{|V||E|} - \frac{1}{|E||V|^2} \frac{1}{d_u d_v} \tag{3}$$

where $S_{VN} = \sum_{(u,v)\in E} S_{VN}^{edge}(u,v)$. This expression decomposes the global parameter of von Neumann entropy on each edge with the relation to the degrees from the connection of two vertexes.

3 Quantum Statistics and Global Entropy Decomposition

The concept of von Neumann entropy arises in the quantum domain. Here, we commence from the Hamiltonian operator in quantum statistics to develop thermodynamic entropy. We then decompose or project the global entropy onto edges using the eigenvectors of normalised Laplacian matrix.

3.1 Thermodynamic Entropy

To connect the normalised Laplacian matrix to statistical mechanics and quantum statistics, we view the eigenvalues of the Laplacian matrix as the energy eigenstates of a system in contact with a heat reservoir. These determine the Hamiltonian and hence the relevant Schrödinger equation which governs the particles in the system. The particles occupy the energy states of the Hamiltonian subject to thermal agitation by the heat bath. The number of particles in each energy state is determined by the temperature, the assumed model of occupation statistics and the relevant chemical potential.

We consider the network as a thermodynamic system of N particles with energy states given by normalised Laplacian matrix $\tilde{L}$, which is immersed in a heat bath with temperature T. The ensemble is represented by a partition function $Z(\beta, N)$, where β is inverse of temperature T. When specified in this way, the thermodynamic entropy is given by,

$$S = k_B \left[\frac{\partial}{\partial T} T \log Z\right]_N \tag{4}$$

with the corresponding chemical potential μ as,

$$\mu = -k_B T \left[\frac{\partial}{\partial N} \log Z\right]_\beta \tag{5}$$

The statistical properties of particles in the network are determined by the partition functions associated with different energy level occupation statistics. In this way, thermodynamic quantities, such as entropy, can characterise the network structure.

3.2 Bose-Einstein Edge Entropy

Bose-Einstein statistics apply to indistinguishable bosons which can aggregate in the same energy state. For a system with a varying number of particles N and a chemical potential μ, the Bose-Einstein partition function is

$$Z_{BE} = \det\left(I - e^{\beta\mu}\exp[-\beta\tilde{L}]\right)^{-1} = \prod_{i=1}^{V}\left(\frac{1}{1-e^{\beta(\mu-\varepsilon_i)}}\right) \tag{6}$$

From Eq. (4), the corresponding entropy is

$$S_{BE} = -\mathrm{Tr}\Big\{\log[I - e^{\beta\mu}\exp(-\beta\tilde{L})]\Big\} - \mathrm{Tr}\Big\{\beta[I - e^{\beta\mu}\exp(-\beta\tilde{L})]^{-1}(\mu I - \tilde{L})e^{\beta\mu}\exp(-\beta\tilde{L})\Big\} \tag{7}$$

The entropy depends on the chemical potential for the system and hence the number of particles in the system. The equivalent density matrix for the system of particles is given by

$$\boldsymbol{\rho}_{BE} = \frac{1}{\mathrm{Tr}(\boldsymbol{\rho}_1) + \mathrm{Tr}(\boldsymbol{\rho}_2)} \begin{pmatrix} \boldsymbol{\rho}_1 & 0 \\ 0 & \boldsymbol{\rho}_2 \end{pmatrix} \tag{8}$$

where

$$\boldsymbol{\rho}_1 = -\Big(\exp[\beta(\tilde{L} - \mu I)] - I\Big)^{-1}$$
$$\boldsymbol{\rho}_2 = \Big(I - \exp[-\beta(\tilde{L} - \mu I)]\Big)^{-1}$$

To compute the edge entropy projection for a system with Bose-Einstein statistics, we exploit the spectral decomposition of the normalised Laplacian matrix. The Bose-Einstein entropy can be written as

$$S_{BE}^{edge}(u,v) = \sum_{i=1}^{|V|} \sigma(\varepsilon_i)\varphi_i\varphi_i^T \tag{9}$$

where

$$\sigma_{BE}(\varepsilon_i) = -\sum_{i=1}^{V} \log\Big(1 - e^{\beta(\mu-\varepsilon_i)}\Big) - \beta\sum_{i=1}^{V} \frac{(\mu-\varepsilon_i)e^{\beta(\mu-\varepsilon_i)}}{1 - e^{\beta(\mu-\varepsilon_i)}}$$

3.3 Fermi-Dirac Edge Entropy

Fermi-Dirac statistics apply to indistinguishable fermions with a maximum occupancy of one particle in each energy state. According to the Pauli exclusion principle, no further particles can be added to states that are already occupied. The partition function for a system subject to Fermi-Dirac occupation statistics is

$$Z_{FD} = \det\Big(I + e^{\beta\mu}\exp[-\beta\tilde{L}]\Big) = \prod_{i=1}^{V}\Big(1 + e^{\beta(\mu-\varepsilon_i)}\Big) \tag{10}$$

with associated entropy given by

$$S_{FD} = \mathrm{Tr}\Big\{\log[I + e^{\beta\mu}\exp(-\beta\tilde{L})]\Big\} - \mathrm{Tr}\Big\{\beta[I + e^{\beta\mu}\exp(-\beta\tilde{L})]^{-1}(\mu I - \tilde{L})e^{\beta\mu}\exp(-\beta\tilde{L})\Big\} \tag{11}$$

Similarly, the density matrix for the system is

$$\boldsymbol{\rho}_{FD} = \frac{1}{\mathrm{Tr}(\boldsymbol{\rho}_3) + \mathrm{Tr}(\boldsymbol{\rho}_4)} \begin{pmatrix} \boldsymbol{\rho}_3 & 0 \\ 0 & \boldsymbol{\rho}_4 \end{pmatrix} \tag{12}$$

where

$$\boldsymbol{\rho}_3 = \left(I + e^{-\beta\mu} \exp[\beta\tilde{L}] \right)^{-1}$$
$$\boldsymbol{\rho}_4 = \left(I + e^{\beta\mu} \exp[-\beta\tilde{L}] \right)^{-1}$$

Therefore, the corresponding edge entropy decomposition is,

$$S_{FD}^{edge}(u,v) = \sum_{i=1}^{|V|} \sigma(\varepsilon_i)\varphi_i\varphi_i^T \tag{13}$$

where

$$\sigma_{FD}(\varepsilon_i) = \sum_{i=1}^{|V|} \log\left(1 + e^{\beta(\mu-\varepsilon_i)}\right) - \beta \sum_{i=1}^{|V|} \frac{(\mu-\varepsilon_i)e^{\beta(\mu-\varepsilon_i)}}{1 + e^{\beta(\mu-\varepsilon_i)}}$$

4 Experiments and Evaluations

In this section, we describe the application of the above methods to the analysis of interregional connectivity structure for fMRI activation networks for normal and Alzheimer's patients. We first examine the dependence of the quantum edge entropy components on node degree and temperature and compare their performance with von Neumann entropy. Then we apply edge entropy-based analysis to distinguish between different stages in the development of Alzheimer's disease, and fMRI data for normal subjects. We explore whether we can identify specific inter-regional connections and regions in the brain associated with the neuro-degeneration caused by the onset of Alzheimer's disease. To simplify the calculations, the Boltzmann constant is set to unity in our experiments.

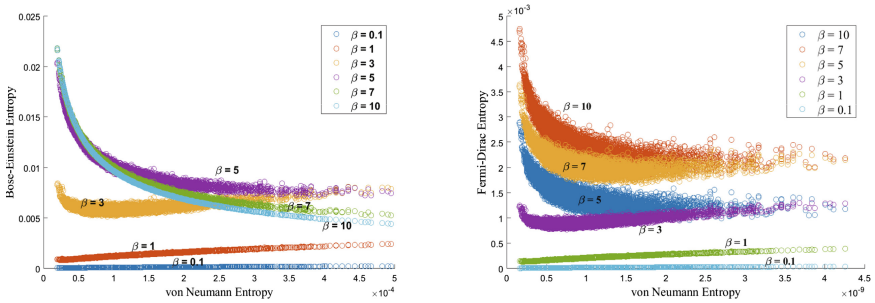
4.1 Dataset

The fMRI data were obtained from the ADNI initiative [9]. fMRI images of subjects brains were taken every two seconds and are used to compute the Blood-Oxygenation-Level-Dependent (BOLD) signals for different anatomical brain regions. To do this the fMRI voxels were aggregated into larger regions of interest (ROIs). The different ROIs correspond to different anatomical regions of the brain and are assigned anatomical labels to distinguish them. There are 96 such anatomical regions in each fMRI image. The correlation between the average time series in different ROIs represents the degree of functional connectivity between regions which are driven by neural activities [8].

We construct a graph to represent the pattern of activities using the cross-correlation coefficients for the average time series for pairs of ROIs. We create an undirected edge between two ROI's if the cross-correlation co-efficient between the time series is in the top 40% of the cumulative distribution. This cross-correlation threshold is fixed over all of the available data, which provides an optimistic bias for constructing graphs. Those ROIs that have missing time series data are discarded. Subjects fall into different categories according to the degree of severity of the disease, there are normal subjects, those with early mild cognitive impairment, those with late mild cognitive impairment and those with full Alzheimer's. The data supplied included 30 subjects with Alzheimer's disease (AD) and 38 normal, healthy control subjects.

4.2 Experimental Results

We first investigate the relationship between the mean edge entropy computed using quantum statistics and von Neumann entropy. Figure 1 shows the edge entropy with varying temperatures. Both statistical entropies exhibit a transition in behaviour with respect to the von Neumann entropy with varying temperature. For example, at the high temperature ($\beta = 0.1$), both quantum entropies are roughly in linear proportion to the von Neumann entropy. As the temperature reduces, they take on an approximately exponential dependence. At low temperature, the quantum edge entropies decrease monotonically with the von Neumann edge entropy ($\beta = 10$). Therefore, at high temperature, the quantum and von Neumann edge entropies are proportional, while at low temperature they are in inverse proportion.



(a) Bose-Eistein Statistics (b) Fermi-Dirac Statistics

Fig. 1. Scatter plot of edge entropies compared to the von Neumann entropy with different value of temperatures.

However, the spread as measured by the variance of the quantum edge entropies corresponding to a fixed von Neumann entropy is also revealing. In the Bose-Einstein case, the spread of edge entropies about the mean is narrow, while in the Fermi-Dirac it exhibits a broader and more scattered pattern.

This effect is most obvious in the high-temperature region. The reason for this is that the networks possess some internal cluster or community structure. Since Bose-Einstein statistics preferentially sample the lower energy levels of the network eigenvalue spectrum, it is more susceptible to strong community structure. On the other hand, Fermi-Dirac statistics are more sensitive to a wider range of eigenvalues and are hence sensitive to both the to the mean and variance of the eigenvalue distribution.

We also apply the different edge entropy computations to fMRI brain networks, with the aim of determining which anatomical regions play the strongest role in the development of Alzheimer's disease. Figure 2 the different edge entropy distribution for the Alzheimer's disease (AD) and healthy control (Normal) samples. Compared to the von Neumann entropy which does not show a clear difference in distributions between the two groups, the quantum entropies better distinguish the detailed distribution of edge entropy. The edge entropy in the case Alzheimer's disease tends towards lower values. This observation is more palpable in the cases of the Bose-Einstein and Fermi-Dirac edge entropy distributions, as shown in Fig. 2(b) and (c), with more edges tending to occupy the low entropy region. Moreover, the Bose-Einstein edge entropy exhibits better separation between the healthy and Alzheimer's groups compared to that for the Fermi-Dirac distribution, since here the non-overlapping area is much larger.

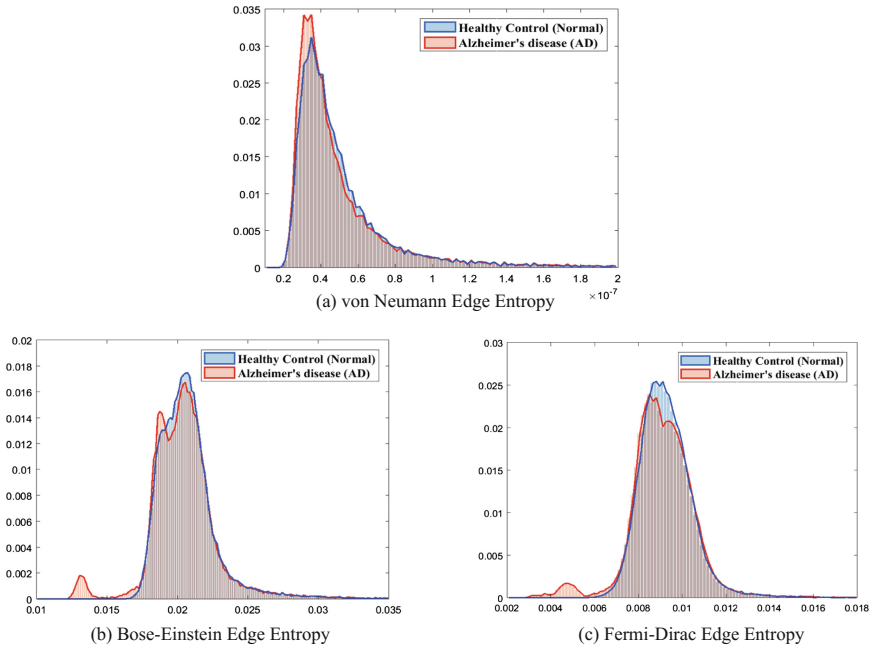


Fig. 2. Edge entropy distribution of fMRI networks with (a) von Neumann entropy, (b) Bose-Einstein statistics and (c) Fermi-Dirac statistics. Two groups of patients, Alzheimer's disease (AD) and healthy control (Normal).

Identifying diseased regions in the brain is also important. Several studies have shown that different anatomical structures can be analysed using the properties of the corresponding ROIs, and are important for understanding brain disorders [10,11]. Here, we use the difference in standard deviation for the quantum entropy to identify the sources of significant variance between AD and HC groups. Figure 3 plots the greatest variance of edge entropy for different anatomical regions (nodes). The entropic measurements in the brain areas, such as the Paracingulate Gyrus, Parahippocampal Gyrus, Inferior Temporal Gyrus and Temporal Fusiform Cortex, suggest that subjects with AD experience loss of interconnection between these regions in their brain network during the progression of the disease.

As listed in Table 1, the ten anatomical regions with the largest entropy differences for subjects with the full AD are Paracingulate Gyrus, Parahippocampal Gyrus, Temporal Fusiform Cortex, etc. This result is consistent with the previous study reported in [11,12]. For example, the parahippocampal gyrus has consistently been reported as being vulnerable to pathological changes in Alzheimer's disease (AD), which is closely related to entorhinal and perirhinal subdivisions as the most heavily damaged cortical areas for the disease [13]. The Frontal Medial Cortex and Temporal Fusiform Cortex are memory-related cognitive areas. They are severely damaged by Alzheimer's disease and affect recognition memory for faces. Overall, the loss of connection between these brain regions results in significant functional impairment between healthy subjects and patients with the AD.

Table 1. Top 10 ROIs with the most significant difference in edge entropy between the Alzheimer's disease (AD) and Health Control (Normal) groups.

Index	ROI	ROI
1	Inferior Temporal Gyrus Left (14)	Temporal Fusiform Cortex Left (37)
2	Frontal Medial Cortex Left (25)	Frontal Medial Cortex Right (73)
3	Paracingulate Gyrus Left (27)	Paracingulate Gyrus Right (75)
4	Parahippocampal Gyrus Left (34)	Temporal Fusiform Cortex Left (37)
5	Parahippocampal Gyrus Left (34)	Parahippocampal Gyrus Right (82)
6	Temporal Fusiform Cortex Left (37)	Temporal Fusiform Cortex Right (85)
7	Temporal Fusiform Cortex Left (37)	Temporal Fusiform Cortex Right (86)
8	Inferior Temporal Gyrus Right (63)	Temporal Fusiform Cortex Right (86)
9	Planum Polare Right (92)	Heschl's Gyrus Right (93)
10	Heschl's Gyrus Right (93)	Planum Temporale Right (94)

In conclusion, both statistical methods and von Neumann edge entropies can be used to represent changes in network structure. Compared to the von Neumann edge entropy, quantum edge entropies are more sensitive to sample variance associated with the degree distribution. At high-temperature region, the quantum statistics have similar degree sensitivity. However, at low-temperature,

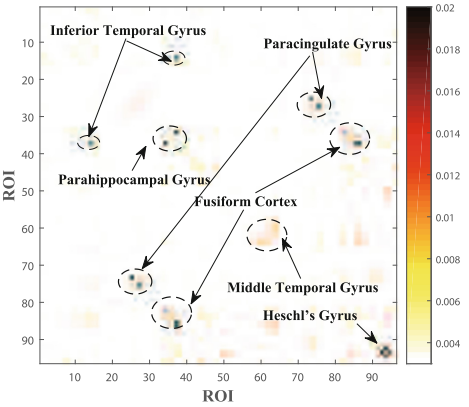


Fig. 3. Significant differences between edge entropy associated with diseased areas in the brain. We use the standard deviation of quantum entropy to identify the divergence between AD and HC groups for each edge.

Bose-Einstein statistics reflect strong community structure while Fermi-Dirac statistics are more suitable for representing a detailed structure of the degree distribution.

5 Conclusion

In this paper, we show how to decompose the global network entropies resulting from quantum occupation statistics onto the constituent edges of a graph. We refer to the resulting quantum statistical quantities as Bose-Einstein and Fermi-Dirac edge-entropies. The method uses the normalised Laplacian matrix as the Hamiltonian operator of the network to compute the corresponding partition functions. We undertake experiments to analyse the quantum edge entropies and compare them to their von Neumann counterparts. Experiments reveal that both the Bose-Einstein and Fermi-Dirac edge entropy distributions can effectively in characterising detailed variations in the network structure. They both outperform the von Neumann entropy in this respect. Finally, we apply this novel method to provide insights into the neuropathology of Alzheimer's disease. The quantum edge entropy distribution is capable of discriminating between subjects suffering from Alzheimer's and healthy subjects.

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