Markov Processes and Brain Network Hubs*

M Ram Murty and Asuri Narayan Prasad

Current concepts of neural networks have emerged over two centuries of progress, beginning with the neural doctrine to the idea of neural cell assemblies. Presently, neural network models involve distributed neural circuits of nodes, hubs, and connections that are dynamic across different states of brain function. Advances in neurophysiology, neuroimaging, and the field of connectomics have given impetus to the application of mathematical concepts of graph theory. Current approaches do have limitations and inconsistencies in the results they achieve. We model the neural network of the brain as a directed graph and attach a matrix (called the Markov matrix) of transition probabilities (determined by the synaptic strengths) to every pair of distinct nodes, giving rise to a discrete Markov process. We postulate that the network hubs are the nodes with the highest probabilities given by the stationary distribution of Markov theory. We also derive a new upper bound for the diameter of a graph in terms of the eigenvalues of the Markov matrix.

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1. Introduction

The human brain (along with its emergent functions) seems to be the final frontier of science. This exploration has been difficult largely due to an inadequacy of tools. Now, in the 21st century, we have made some technological progress towards the understanding of neural networks, and in this endeavor, the mathematical branch of graph theory has proved to be useful as a language to model the inner cerebral architecture.

In this article, we propose that the firing of neurons or, more pre-

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cisely, neural assemblies, can be modeled as a Markov process (we will review basic Markov theory in Section 5). This idea is not new and has been proposed earlier by others (see, for example, Chen *et al.* [1] and Escola *et al.* [2]). The novelty of this article is to apply the main theorems of Markov chains to determine their implications for our understanding of brain networks and to identify 'brain hubs'. We will model these networks as directed graphs, and so subtler aspects of Markov theory have to be invoked. It is not the adjacency matrix (or connectivity matrix, as it is called in neuroscience) that plays a central role, but rather what we call the Markov matrix of the graph, where each connecting directed edge carries a certain probability weight. The idea of using Markov models to describe neural networks is not new and has been considered in earlier works such as [3] and [4]. The novelty here is to introduce the spectral theory of the Markov matrices, which play a central role in determining many of the graph's properties, such as the diameter of the network (see Theorem 7.2 below). Markov theory seems ideally suited to study a neural network since it embodies two of its fundamental properties: recurrence and emergence. This latter property is often described poetically as "the whole is greater than the sum of the parts."

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At the end of our article, we try to package the information of the neural network into a 'zeta function', which is technically a matrix of functions. The study of this zeta function, motivated by analogies of other zeta functions in mathematics, may be of value in the evolution of a mathematical theory of neural networks. As we have aimed to make this article accessible to students interested in mathematics and neuroscience, we will provide a brief historical overview from a neuroscience perspective.

One of our goals is to initiate a dialogue between certain questions arising in neuroscience and problems and results in (directed) graph theory. Classically, standard graph theory focused largely on undirected graphs. In the neural network context, many processes can be modeled only using directed graphs. Thus, classical graph theory may need revision to include potential applications

in neuroscience. An aspect of this perspective is evident in Theorem 7.2 below.

2. Historical Background to the Concepts of Neural Networks

Our understanding of brain function over the last two hundred years owes a lot to the concept of the neuronal doctrine, extending from the work of Santiago Ramón y Cajal and others. This states that the structural and functional unit of the nervous system is the individual neuron [5]. Through a reconstructive process involving single neurons and their connections, some aspects of the design logic underlying the structure and function of neural pathways in the nervous system were deciphered. The excessive focus on the single neuron, its electrophysiology, and behavior, however, detracts from the ability to develop a deeper understanding that would account for brain function in behavioral or cognitive states associated with health and disease [6]. The neural connectome (that is, a complete map of neural connections in the nervous system of a given species) may behave in ways that are dependent on the nature and complexity of the network that has been acquired in the evolutionary process, from a microscale with a few hundred neurons to several million in the human brain. Thus, it is important to conceptualize a neuronal hub or nodes in a microscale network as involving individual neurons or a few neurons in a network. Or, we can view this as specialized neuronal assemblies of groups of neurons or even regions that go to form a connectome in the human brain connectome. We will elaborate on this a little further in the next section.

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Over the last hundred years, the frameworks have moved from the conceptual topographically organized receptive fields in cortical 'columns' described by Mountcastle, by Hubel and Wiesel, to the idea that the single neuron was not only the anatomical and functional unit of the brain but also its perceptual unit. However, this approach could not explain the finding that neurons can engage in intrinsic and emergent functions unrelated to sensory stimuli or motor actions. It was Cajal's disciple, Rafael Lorente de Nó, who

argued that the structural design of many parts of the nervous system is one of recurrent connectivity, where neuronal signals can reverberate among groups of neurons [7]. This idea was further developed by Donald Hebb [8], who proposed in 1949 the idea of 'cell assemblies' where neural circuits worked by sequentially activating groups of neurons, where recurrent and reverberating patterns of neuronal activation occurring within these closed loops would be responsible for generating the various states of brain function. This foundational work is often described as being on par with Darwin's *Origin of the Species.* This work presented a neurological basis for human behavior and what is called Hebb's law that "neurons that fire together, wire together" is now a fundamental mantra of neuroscience. This law has also led to the neuroplasticity thesis of the human brain. In essence, the brain has the capacity to change itself. Further modification of these ideas came about with the development of electroencephalography and the identification of spontaneous oscillatory activity in neurons.

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The concept of a neural network is further supported by anatomical evidence that neuronal assemblies give rise to a connectivity matrix that encodes communication between neurons or neuronal assemblies. That is, each neuron or neuronal assembly receives inputs from many other neurons or neuronal assemblies while sending its outputs to large populations of cells, and this process is encoded in the matrix. The term 'neural network' model is one made up of distributed neural circuits in which neurons or neuronal assemblies are abstracted into nodes, linked by connections that change according to learning rules.

Neural network assemblies fall into two basic types: feedforward networks, which are governed by one-way connections, and recurrent networks, in which feedback connectivity is dominant. Rather than fixed structure assemblies, it is more likely that a third type of neural network can be conceptualized to operate within biological organ systems in more dynamic states (that are stochastic, not deterministic), permitting the allocation of weights to be asymmetric and exhibiting transient dynamical patterns without

stable states [9]. The asymmetry in the synaptic connectivity matrix naturally endows these models with temporally organized activity without necessarily requiring an input signal. Within such networks, individual neurons acquire flexibility in participating in different networks at different times. This combinatorial flexibility [8], a consequence of synaptic plasticity, permits the modular composition of small assemblies into larger ones, within which neural circuits that are constantly in flux give rise to and encode emergent properties such as time dependence, providing different time stamps to events as they arise [9].

This suggests that we apply continuous-time Markov theory to model the network. But then, this would require explicit knowledge of the transition probability functions, as functions of time. We indicate below how the main theorem of continuous time Markov theory can be used. Future research in neuroscience could determine the nature of these transition functions that can then be applied to determine hubs using such a model.

An approach to the analysis of neural networks and connectivity matrices in the brain, as visualized by current neurophysiological and neuroimaging technologies (EEG, high-density arrays, magnetoencephalography, tractography and anisotropy, functional neuroimaging), is a mathematical one using graph theory that has become central to the identification of network hubs. In this article, we inject both discrete and continuous theories of Markov chains to study brain networks. We also propose that one can go in the reverse direction and reconsider large tracts of classical graph theory from the brain network perspective and derive new results essential to our understanding of these vast networks within networks ('worlds within worlds') that reside in the human brain. Theorem 7.2 below is an example of this symbiotic theme where eigenvalues of the Markov matrix (and not the adjacency matrix, as is customary in spectral graph theory) are related to the diameter and radius of the graph.

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3. Neural Networks in Disease States: Epilepsy as a Network Disorder

Data from clinical, neuropathology, and imaging studies suggest that there is a pervasive disorganization of neural networks in patients with epilepsy.

Data from clinical, neuropathology, and imaging studies suggest that there is a pervasive disorganization of neural networks in patients with epilepsy [10]. Imaging studies have shown atypical hub organization in epilepsy relative to controls, identified associations between hub topography and cognitive dysfunction, and suggested the utility of hub mapping for postsurgical outcome prediction [11] [12].

The patterns of disrupted organizations within networks in patients with epilepsy are described for patients with both focal and generalized epilepsy [13]. These are influenced by several variables, including patient age, age at seizure onset, and disease duration. There is preliminary but compelling evidence that indicates that large-scale network abnormalities lead to the complex effects in the form of cognitive impairment symptoms in epilepsy, particularly in executive functioning, semantic and retrograde memory, and naming.

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While a regional loss in connectivity has been demonstrated in focal epilepsy (temporal lobe epilepsy, TLE), there appear to be measurable perturbations in other parts of the neural networks that show increased clustering and shorter path lengths [14]. Despite regional connectivity loss, it is observed that the small-world properties of the network remained spared. Network analysis has been effectively used to predict treatment resistance, response to surgery, failure of surgery, and the effects on cognition and behavior (pre- and post-surgery in persons with epilepsy (PWE)) [12].

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4. Graph Theory as Applied to Neural Networks and the Concept of Hubs

The entire neural network and its connections in the human brain are referred to as the 'connectome'. Here, the concept of the connectome is operative on a macroscale. Nodes represent dis-

tinct neural elements, such as specialized neuronal assemblies, and edges represent connections between nodes. Developmental processes determine how connections within this network develop, resulting in certain neural assemblies within regions possessing a large number of network connections, which are putatively marked as 'network hubs'.

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In the human brain, visualization of the microscale is not possible, even with high-resolution imaging. Using methods of white matter tractography and resting-state fMRI, it has been possible to construct functional and structural connectomes. These are quantitative representations of brain architecture as neural networks, comprised of nodes and edges. Connectomes, typically depicted as matrices or graphs, possess topological properties that inherently characterize the strength, efficiency, and organization of connections between distinct brain regions.

These nodes and hubs functionally and on account of their location serve to direct a large fraction of signaling traffic within the brain and are implicated in many neurological and psychiatric disorders, such as epilepsy, autism, etc. [15] Such hubs are vulnerable to pathological insults and consequently develop structural alterations that enhance network excitability.

Multicellular and macroscale phenomenology generated by such network arrangements and rearrangements, and the corresponding emergent properties that lead to an understanding of brain functions in health, are currently a focus of neural network research. See, for example, [16] and [17].

The application of graph theory to the analysis of network connectivity matrices has already progressed despite the many limitations of current methodologies employed and the variability of results across different modalities employed in studying connectivity within the brain. In this context, a *connectome* is defined as a "comprehensive structural description of the network of elements and connections of a given nervous system." Connectomics [18] is then the branch of neuroscience focused on reconstructing the connectome of various organisms. To study the structure of

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these networks to understand and explain the divergent findings from imaging studies, connectivity, and network analysis, several authors [15] [19] have introduced the mathematical theory of graphs as a framework. The ambitious 'human connectome project' [18] consists of mapping all the neural connections of the brain.

Towards this goal, the concept of 'hubness' and 'hubs' in various contexts is the first step. For instance, different forms of connectivity of the brain regions, such as structural connectivity and functional connectivity, are described in [19]. Using this modeling, many authors have defined the notion of *hubs* as being "brain regions with high connectivity to other parts of the brain" and "situated along the brain's most efficient communication pathways." The mathematics of graph theory was then proposed as a means to identify the hubs using various measures of *centrality*. For instance, *degree centrality*, *betweenness centrality* and *eigenvector centrality* can be measured using graph theory. Eigenvector centrality in particular arises by associating with the neural network a discrete-time Markov process (similar to the Google PageRank algorithm) and identifying the hubs as those nodes with the highest probabilities arising from the stationary distribution of irreducible Markov chains. In this model, a transition probability is associated with each pair of nodes i, j and is equal to the reciprocal of the number of outgoing edges from i to j. (We are assuming at most one edge between any pair of nodes. If there are multiple edges, one can define the transition probability as the ratio of the number of directed edges from i to j divided by the total number of directed edges emanating from i.) Keeping in mind that our nodes represent neural assemblies, all synaptic assemblies are not the same, and, as their efficiency is determined by synaptic strength [20], the discrete Markov model may not fully identify all hubs. We, therefore, propose a continuous-time Markov model that takes into account synaptic strength (which can be measured using various neuroimaging and electrophysiological modalities) and allows it to evolve over time to accommodate neural plasticity. This gives rise to a continuous Markov

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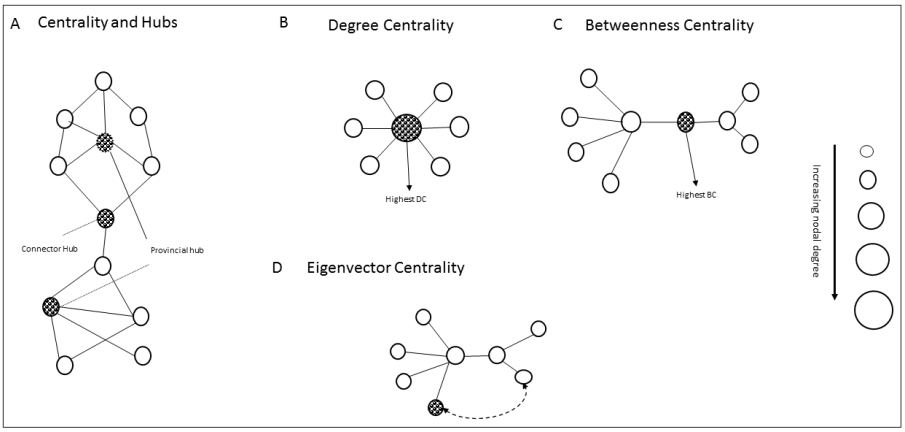

Figure 1. Various concepts of nodal centrality.

process, which can be studied using methods different from the discrete case (described below). As hubs are often implicated in the generation of epileptic seizures and may be involved in other brain disorders due to their vulnerability, a better delineation of these neuronal assemblies may lead to a more precise surgical intervention and/or the identification of targets that are affected selectively in disease states and lead to early recognition of such pathology in association with neuro-psychiatric symptoms.

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Let us briefly discuss degree centrality and betweenness centrality. (For basic notions of graph theory, the reader can refer to [21].) If we model the brain network using graph theory, the nodes (or vertices) of the graph G correspond to brain regions, and the directed edges represent connections between regions, as measured by various neurophysiological methods and imaging techniques such as EEG, MEG, fMRI, and MRI tractography. There is no loss of generality in assuming our graph G is connected. That is, given any two distinct nodes x, y, there is a directed path from x to y. In such a directed graph, one has the notion of a 'directed distance' between two nodes x, y as the length $d(x, y)$ of the shortest directed path from x to y. Following the usual terminology of graph theory, the *eccentricity* $e(x)$ of a node x is simply

$$e(x) := \max_{y \in G} d(x, y).$$

The diameter and radius of the graph are the maximum and minimum nodal eccentricities, respectively. One can use eccentricity to identify hubs, leading to the notion of betweenness centrality.

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The *outdegree* of a node x is the number of edges emanating from x and is denoted as $d^+(x)$. The *indegree* is the number of edges entering into the node x and is denoted $d^-(x)$. If the graph is undirected, $d^+(x) = d^-(x)$ and the *degree* is then this common value. Royer and others have modeled the brain network as an undirected graph and introduced several measures of *centrality* such as *degree centrality* (nodes with the largest degree), *betweenness centrality* (discussed above) and *eigenvector centrality* (discussed below). Each of these measures of centrality (see *Figure* 1) identifies hubs in different ways [15]. In this article, we propose a new model of the brain network as a directed graph and a notion of centrality that emerges viewing this network as both a discrete and continuous Markov process. Hubs are then identified using these two perspectives.

5. The Discrete-Time Markov Model

In the simplest model discussed in the literature, two nodes i and j of the graph G associated with the brain's neural network are deemed adjacent if there is a directed edge from i to j.

In the simplest model discussed in the literature, two nodes i and j of the graph G associated with the brain's neural network are deemed adjacent if there is a directed edge from i to j. The discrete Markov process that is then associated with G is given by the matrix P of transition probabilities p_{ij} which is equal to the reciprocal of the outdegree of i. If there is no directed edge from i to j, the probability is set to zero. If there are multiple edges from i to j, one can set the probability to be the total number of edges from i to j divided by the outdegree of i. It is convenient to call P the Markov matrix associated with G. Let us note that our matrix P is *row stochastic*, that is, the sum of the entries in each row adds up to 1 since it represents the probability that the process moves from state i to some other state. (One can consider a more general situation where P is the matrix of transition probabilities, which are not necessarily determined by the indegrees and outdegrees.)

Our hypothesis that G is strongly connected is equivalent to say-

ing that we have what is called an *irreducible Markov chain*. As the number of neurons (or neuronal assemblies) is finite, we conclude that all nodes are recurrent and non-null, in the sense of Markov theory (for definitions of these terms, see for example, the lemma on page 225 of [22]). In this setting, the fundamental theorem of Markov chains (see page 227 of [22]) applies, and there is a unique stationary distribution $\mathbf{v}$ satisfying

$$\mathbf{v}P = \mathbf{v}.$$

This reduces the problem of determining hubs into a problem of linear algebra, which is easily solved. In other words, the i-th coordinate of $\mathbf{v}$ encodes the probability that the stationary probability of the process being in i in the limit. Thus, hubs can be identified as those nodes with the highest probabilities encoded in $\mathbf{v}$. This is eigenvector centrality in a nutshell (and it is the same theoretical foundation for the Google PageRank algorithm).

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6. The Continuous-Time Markov Model

In the continuous model, we associate probability functions $p_{ij}(t)$ as a function of time t. These could be functions giving the synaptic strength between the neural assemblies indicated by i and j. We thus get a matrix $P(t)$ whose entries are functions of time t. We will assume that our matrix entries are differentiable functions of t. By the fundamental theorem of continuous-time Markov chains, one can associate a matrix Q (called the generator matrix) such that

$$P(t) = \exp(tQ),$$

and the stationary distribution $\mathbf{v}$ of $P(t)$ is determined by solving $\mathbf{v}Q = 0$ (see pages 259–261 of [22]). This is again a problem of linear algebra. The matrix Q has a simple description as a matrix of *transition intensities*:

$$q_{ii} = -p'_{ii}(0) = \lim_{t\to 0} \frac{1 - p_{ii}(t)}{t}, \qquad q_{ij} = q_{ii}p'_{ij}(0), \quad i \neq j.$$

Continuous time Markov theory then implies that $\mathbf{v}P(t) = \mathbf{v}$. In other words, the hubs can again be identified as those coordinates with the highest probabilities encoded by $\mathbf{v}$.

Now, any component-wise positive probability vector can be realized as a stationary distribution of some continuous time and some discrete time Markov chain, in fact in a non-unique manner in both cases (the Monte Carlo Markov Chain algorithm provides an explicit construction). We will therefore work with a discrete time model in the discussion below.

7. The Diameter of the Brain Network

In this section, we will discuss the discrete case and the role the matrix P plays as it relates to questions of classical graph theory. In spectral graph theory, bounds for the diameter of a graph are often derived using eigenvalues of the adjacency matrix. The above analysis, at least in the context of the brain network, suggests that it may be relevant to shift the focus and relate the diameter to the eigenvalues of the Markov matrix P. As P is a matrix of probabilities, it is a non-negative matrix and the celebrated Perron–Frobenius theorem (which we state below) applies. As the sum of the entries of each row of P equals 1, we see that the column vector $\mathbf{J}$ consisting of all 1's is a (right) eigenvector of P with eigenvalue 1. For an irreducible, aperiodic chain, the Perron–Frobenius theorem (see page 240 of [22]) implies that all the other eigenvalues have absolute value strictly less than 1. We call these the non-trivial eigenvalues and define

$\rho :=$ the maximum absolute value of the non-trivial eigenvalues of P.

A matrix is said to be irreducible if if it is not similar via a permutation to a block upper triangular matrix.

Let us recall that a matrix is said to be *irreducible* if if it is not similar via a permutation to a block upper triangular matrix. Applying this definition to our matrix P, this is tantamount to saying that entries of some power of P are all strictly positive.

Theorem 7..1 (Perron-Frobenius)**.** *Suppose that P is a non-negative matrix which is irreducible. Let a_{ij} denote the (i, j)-th entry of P. Then P has a real, positive eigenvalue λ_1 with the following properties.*

(a) *Corresponding to λ_1, there is an eigenvector $\mathbf{x}$ all of whose elements may be taken as positive.*

(b) *Any other eigenvalue α satisfies $|\alpha| \leq \lambda_1$.*

(c) *λ_1 increases when any element of P increases.*

(d) *λ_1 is a simple eigenvalue of P.*

(e) $\lambda_1 \leq \max_j \left(\sum_k a_{jk}\right), \qquad \lambda_1 \leq \max_k \left(\sum_j a_{jk}\right).$

(f) *If P has exactly t eigenvalues of maximum modulus λ_1, then there is a non-singular matrix C such that*

$$C^{-1}PC = \begin{pmatrix} \Lambda & 0 \\ 0 & J \end{pmatrix}$$

where Λ is a $t \times t$ diagonal matrix $\mathrm{diag}(\lambda_1, \lambda_1\zeta_t, ..., \lambda_1\zeta_t^{t-1})$ *with $\zeta_t = e^{2\pi i/t}$ and J is a Jordan matrix whose diagonal elements are all strictly less than λ_1 in modulus. Note that Λ corresponds to a block matrix of period t.*

(g) *If P is aperiodic, then $t = 1$.*

Before proving our theorem, we recall the notion of the *norm* of a matrix A. This is defined as

$$||A|| := \max_{x \neq 0} \frac{||Ax||}{||x||},$$

where $||x||$ denotes the usual Euclidean norm of a vector. If A^T is the transpose of A, then it is easy to see that $||A|| = ||A^T||$. The *condition number*, denoted $\kappa(A)$ of an invertible matrix A is defined as

$$\kappa(A) := ||A||\,||A^{-1}||,$$

where $||A||$ is the norm of the matrix A. The condition number of A is invariant under permutation of its columns and re-scaling them. If A is any non-singular $n \times n$ matrix with real entries, then A^TA is symmetric and positive definite. Therefore, the eigenvalues of A^TA are all real and positive. The *singular values* of A are then defined to be the positive square roots of the eigenvalues of A^TA and we can order them as $\sigma_1 \geq \sigma_2 \geq \cdots \geq \sigma_n > 0$. The condition number of A can be shown to be equal to σ_1/σ_n (see for example pages 280-286 of [23]).

With this interlude, we now apply the Perron–Frobenius theorem to prove:

Theorem 7..2. *Let G be a connected graph with Markov matrix P which is aperiodic with simple eigenvalues. Let* $\mathbf{v}$ *be its unique stationary distribution with components v_j. Then $v_j > 0$ for every j. If C is the matrix whose columns are a basis of eigenvectors of P and $\kappa(C)$ is the condition number of C, then eccentricity of any node i is bounded by* $\max_j(\log v_j)/(\log \rho)$. *Thus, the diameter and radius of G are bounded by*

$$\max_j \frac{\log[\kappa(C)/v_j]}{[\log 1/\rho]}.$$

Proof. Let G have M nodes. Since G is connected, our matrix P is irreducible. The aperiodicity of P implies that $t = 1$ in the Perron–Frobenius Theorem 7..1. As all the eigenvalues are simple, there is a basis of eigenvectors. As P is row stochastic, it has eigenvalue 1 with corresponding eigenvector $\mathbf{J}$. By (e), this must be the largest eigenvalue and by (b), all the other eigenvalues are strictly less than 1 in absolute value. Thus, $\lambda_1 = 1$. Let C be the matrix whose columns are a basis of eigenvectors of P ordered so that the first column is $\mathbf{J}$. Thus, $PC = C\text{diag}(\lambda_1, ..., \lambda_M)$ so that

$$C^{-1}PC = \text{diag}(\lambda_1, ..., \lambda_M), \tag{1}$$

where $\lambda_1 = 1$ and $\lambda_2, ..., \lambda_M$ are the non-trivial eigenvalues. A routine induction argument shows

$$C^{-1}P^nC = \text{diag}(\lambda_1^n, ..., \lambda_M^n),$$

and consequently

$$P^n = C\text{diag}(\lambda_1^n, ..., \lambda_M^n)C^{-1}.$$

Writing $P^n = [p_{ij}^{(n)}]$, $C = [c_{ij}]$ and $C^{-1} = [b_{ij}]$, we have by the rules of matrix multiplication that

$$p_{ij}^{(n)} = \sum_{k=1}^{M} c_{ik}\lambda_k^n b_{kj}. \tag{2}$$

It is easy to see that

$$\sum_{j=1}^{M} |c_{ij}|^2 \leq \|C\|^2, \qquad \sum_{k=1}^{M} |b_{kj}|^2 \leq \|C^{-1}\|^2 \qquad \forall\, i, j. \tag{3}$$

Indeed, the left-hand side of both inequalities in (3) can be viewed as the norms of the vector $e_i C$ and Be_j where e_i and e_j denote the standard basis vectors with zero entries except in the i-th position and j-th position (respectively), where it is equal to 1. Then (3) is immediate from the definition of the norm and the observation that $\|C^T\| = \|C\|$.

Noting that $\lambda_1 = 1$ and all the other non-trivial eigenvalues have absolute value strictly less than 1, we see from (2) that

$$\lim_{n\to\infty} p_{ij}^{(n)} = c_{i1} b_{1j}.$$

Recalling that the first column of C is the eigenvector $\mathbf{J}$ (rescaled), we see that c_{i1} does not depend on i and is a fixed scalar. We can therefore write $v_j = c_{i1} b_{1j}$. Thus, we see from (2) that

$$p_{ij}^{(n)} = v_j + \sum_{k=2}^{M} c_{ik} \lambda_k^n b_{kj}.$$

Applying the Cauchy–Schwarz inequality to the sum on the right and using (3), we deduce

$$|p_{ij}^{(n)} - v_j| \leq \kappa(C)\rho^n. \tag{4}$$

The components of the vector $\mathbf{v} = (v_1, ..., v_M)$ are the stationary probabilities of the process, and so the components are non-negative and add up to 1. The Perron–Frobenius theory, however, implies that the v_j's are all strictly positive. This can be seen very easily without appealing to the theory as follows. From (1), we have $C^{-1}P = \text{diag}(\lambda_1, ..., \lambda_M)C^{-1}$ and the first row of C^{-1} is the vector (b_{1j}). Keeping in mind that $\lambda_1 = 1$, the equation $C^{-1}P = \text{diag}(\lambda_1, ..., \lambda_M)C^{-1}$ implies that the row vector $\mathbf{v} = (v_1, ..., v_M)$ is a left eigenvector of P with eigenvalue 1. Hence, $\mathbf{v}P = \mathbf{v}$ and by induction $\mathbf{v}P^n = \mathbf{v}$ for all $n \geq 1$. As the sum of the v_i's equals 1, there is a k_0 such that $v_{k_0} > 0$. From $\mathbf{v} = \mathbf{v}P^n$, we have

$$v_j = \sum_{k=1}^{M} v_k p_{kj}^{(n)} \geq v_{k_0} p_{k_0 j}^{(n)}, \tag{5}$$

for any n. As our graph is connected, there is an n_0 such that $p_{k_0 j}^{(n_0)} > 0$. Choosing $n = n_0$ in (5), we deduce $v_j > 0$. Returning to (4), we see that $p_{ij}^{(n)} > 0$ if $v_j - \kappa(C)\rho^n > 0$ which is the case if $1/v_j < \kappa(C)^{-1}(1/\rho)^n$. In other words, if $n > (\log \kappa(C)/v_j)/\log(1/\rho)$, we have $p_{ij}^{(n)} > 0$, which means there is a path of length n from i to j. Since the eccentricity of a node x is the maximum of $d(x, y)$ as y ranges over the nodes of the graph G, the eccentricity is bounded by

$$\max_j \frac{\log[\kappa(C)/v_j]}{[\log 1/\rho]}.$$

As the diameter and radius are the maximum and minimum of the nodal eccentricities, the last assertion is immediate. This completes the proof. □

From the expression of Theorem 7..2 as

$$\frac{\log \kappa(C)/v_j}{\log 1/\rho},$$

we see that to minimize the eccentricity and thus bound the radius, one first needs to maximize the denominator and thus minimize ρ. We then need to minimize the numerator, and this means to maximize v_j. In other words, the 'leader hub' can be used to bound the radius.

Another remark is that if C is an orthogonal matrix, which is the case if P is symmetric, then $\kappa(C)$ is equal to 1. It is possible to replace $\kappa(C)$ with a 'spectral bound' depending only on the eigenvalues of P. This work involves another approach and is the subject matter of the forthcoming paper [24].

The problem of classification of graphs in which ρ is minimized is a new problem of graph theory and has not been studied before, except in some very special cases like regular graphs in which the degree of every node is the same.

The problem of classification of graphs in which ρ is minimized is a new problem of graph theory and has not been studied before, except in some very special cases like regular graphs in which the degree of every node is the same. But in this case, the adjacency

matrix and the Markov matrix are essentially the same apart from a scaling factor. Thus, the study of brain networks using graph theory leads to some new and interesting problems in mathematics hitherto unexamined.

One additional comment is worth noting. In our theorem, we assumed that all the eigenvalues were simple. A random stochastic matrix has simple eigenvalues, and so, generically, this is not a stringent hypothesis. One can treat the multiple eigenvalue case, but the details are a bit more involved.

8. Application of the Model to the Nematode *Caenorhabditis Elegans*

As a preliminary application of the theory, we applied our discrete Markov model to the connectivity matrix of the neural network of the microscopic roundworm *C. elegans*, which is available from the Dynamic Connectome Lab[1].

The *C. elegans* connectome in the hermaphrodite has 302 neurons, while the adult male has been identified to have 385 neurons. After removing neurons with 0 outdegree, a 300×300 matrix was used in this connectomic analysis using the model above. We arrived at the following. The *C. elegans* connectome corresponding to the hermaphrodite chemical network has 165 strongly connected components (SCCs). The largest SCC has 273 neurons, while the second largest SCC has 18 neurons.

The *C. elegans* connectome in the hermaphrodite has 302 neurons, while the adult male has been identified to have 385 neurons.

The number of SCCs comes from the NetworkX library's strongly_connected_components function. This list was then sorted by size. Our mathematical model is consistent with the analysis of Emmons [25]. One can find the functions of the dominant neurons there. An undergraduate student, Aahana Jain at the Indian Institute of Scientific Education and Research (IISER) in Bhopal (India), has given a graphical representation of this data, which we have included as *Appendix* 1 to this article. We have also in-

1 https://www.dynamic-connectome.org/resources

cluded, in *Appendix* 2, a list of the top 20 neurons (according to the stationary distribution output) together with their functions. An expanded discussion of the neural network of the *C. elegans* organism is presented in the recent paper of Emmons [25].

We have also explored the applicability of the proposed approach to the neural network connectome of *Drosophila* (fruitfly) [26] to identify critical neuronal constituents. The findings are the subject of our next article, which demonstrates the applicability of the proposed mathematical approach using Markov theory to more complex connectomes than the *C. elegans* connectome.

9. The Zeta Function of a Finite Network

The quantity ρ, defined as the maximum absolute value of the non-trivial eigenvalues of P played an important role in Theorem 7.2. As can be seen from the theorem, the smaller the value of ρ, the smaller the diameter. This is related to the 'spectral gap' phenomenon, well-known in the theory of Ramanujan graphs and expander graphs as well as the theory of zeta functions in number theory. The concept of a zeta function to study complex phenomena has been a fundamental idea in number theory, algebraic geometry, and graph theory. Inspired by these analogies, a similar concept can be introduced in the context of neural networks. Indeed, if given any (finite) directed graph G, with associated Markov matrix P, we define the zeta function of G as the matrix function

The concept of a zeta function to study complex phenomena has been a fundamental idea in number theory, algebraic geometry, and graph theory. Inspired by these analogies, a similar concept can be introduced in the context of neural networks.

$$Z_G(t) := \exp\left(\sum_{n=1}^{\infty} \frac{P^n t^n}{n}\right).$$

This resembles many zeta functions that appear in algebraic geometry and related areas. But let us note that our zeta function above is a matrix function. The proof of Theorem 7.2 shows that this is a matrix of rational functions. Unlike spectral graph theory, which relates eigenvalues of the adjacency matrix to properties of the graph, the zeta function $Z_G(t)$ relates eigenvalues of the Markov matrix P to hubs of the network. We already saw this phenomenon in Theorem 7.2.

It has also been found that the theory of random graphs is not applicable to understanding the neural network of the brain [27]. For instance, in the case of random graphs, the Erdös–Renyi model shows that the degree distribution is Poisson(see Theorem 3.1 on page 61 of [28]). By contrast, the brain's neural network appears to follow a power law. Empirically, it looks like there is a constant s such that $P(X = k) \asymp k^{-s}$, where $X(v)$ is the random variable giving the degree of a node v. What this suggests is that the degree of randomness of the node follows a zeta distribution in that

$$P(X = k) = \zeta(s)^{-1} k^{-s},$$

for some suitable s with $\zeta(s)$ denoting the Riemann zeta function. This signals a need for a careful study of graphs whose degree distributions follow a power law. In particular, if a_k is a sequence of non-negative real numbers and

$$F(s) := \sum_{k=1}^{\infty} \frac{a_k}{k^s},$$

is its associated Dirichlet series which converges for $\mathrm{Re}(s) > 1$, then the study of random variables X whose distribution is given by

$$P(X = k) = F(s)^{-1} \frac{a_k}{k^s},$$

seems relevant. These are topics for future research.

10. Discussion

We have presented a new model to identify brain network hubs that may be of use in the deeper understanding and treatment of epilepsy and other disorders. As various modalities of measurement are available, it should be possible to clinically test or at least simulate the validity of this hypothesis. The nature of functions describing synaptic strength is studied in [29]. These may be relevant in our continuous-time Markov model. Graph theory can thus be used in these studies in a fundamental way. In this article, we highlighted the importance of Markov theory, but it is

becoming increasingly clear that other deeper chapters of mathematics can be injected into the study of the brain, most notably, the theory of expander graphs. By all descriptions, the wiring of the brain connectome is not random nor regular but "rather characteristic of a small world" [19]. The network exhibits properties of a subclass of graphs called *expander graphs* which have few edges and yet have high connectivity, "an architecture that enables both the specialization and the integration of information transfer at relatively low wiring costs" [19]. On the other hand, our Theorem 7.2 suggests that brain network theory gives rise to new questions in graph theory that have not been studied before.

Finally, we mention the Markov chain tree theorem (see [30]) which provides a way to calculate the stationary distribution of a Markov chain (with a finite number of states) by using rooted spanning trees. It relates the probabilities of transitions between states to the weights of these trees, allowing for the rapid determination of long-term behavior in the chain. The reader can find a simple proof of this in [31].

We hope that these reflections open up a new symbiosis between neuroscience and graph theory. There have been earlier works attempting to relate spectral graph theory to study sociological processes. A nice survey can be found in [32].

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Appendix

Appendix 1: Connectomic Analysis

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The *C. elegans* connectome corresponding to the hermaphrodite chemical network has 165 strongly connected components (SCCs). The largest SCC has 273 neurons, while the second largest SCC has 18 neurons. The remaining 163 SCCs are trivial (size = 1), meaning they are individual nodes that are not strongly connected to any other nodes in the network. This code was used to compute the data in this section.

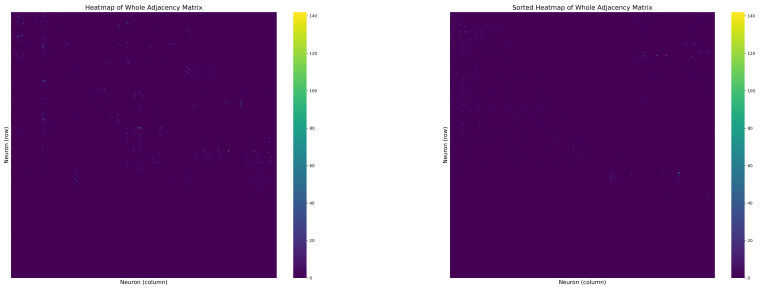
Chemical Synapse: Top Hubs by Stationary Distribution

largest SCC (SCC #1, Size: 274)			**second largest SCC (SCC #2, Size: 18)**		
#	neuron name	stationary dist.	#	neuron name	stationary dist.
1	VD02	0.11823417	1	M4	0.39882527
2	DD01	0.11279257	2	NSML	0.12509934
3	DA02	0.08664755	3	I4	0.11857915
4	VA02	0.07808412	4	M3L	0.09863639
5	VD03	0.05175861	5	M3R	0.08891069
6	VB02	0.03498215	6	NSMR	0.05675731
7	VA03	0.02522818	7	M2L	0.03001504
8	DA05	0.02498552	8	I5	0.02763024
9	DD03	0.02392740	9	I2R	0.01609926
10	DD02	0.02385313	10	I6	0.01096516

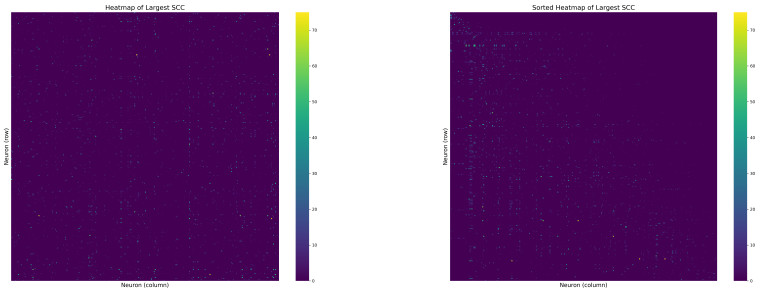
Table 1. Top 10 neurons by stationary distribution in the largest and second largest SCCs.

Heatmaps

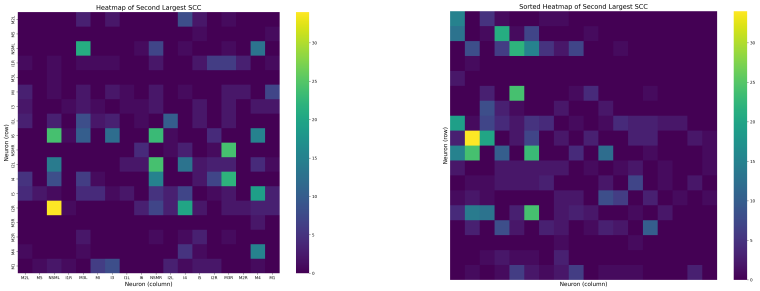
The heatmap on the left corresponds to the full adjacency matrix; on the right, it is sorted by decreasing stationary distribution and decreasing size of the SCC the neurons belong in.



The heatmap on the left corresponds to the largest SCC; on the right, it is sorted by decreasing stationary distribution.



The heatmap on the left corresponds to the second largest SCC; on the right, it is sorted by decreasing stationary distribution.



Appendix 2: Top 20 neurons with the strongest connected components (SCC) organized according to the locomotion/pharyngeal functions

#	neuron name	stationary dist.	Nature of neuron /function	#	neuron name	stationary dist.	Nature of neuron /function
1	VD02	0.11823417	Motor neuron/locom otion	1	M4	0.39882527	Pharyngeal
2	DD01	0.11279257	MN/Locomotion	2	NSML	0.12509934	Pharyngeal
3	DA02	0.08664755	MN/Locomotion	3	I4	0.11857915	Pharyngeal
4	VA02	0.07808412	MN/Locomotion	4	M3L	0.09863639	Pharyngeal
5	VD03	0.05175861	MN/Locomotion	5	M3R	0.08891069	Pharyngeal
6	VB02	0.03498215	MN/Locomotion	6	NSMR	0.05675731	Pharyngeal
7	VA03	0.02522818	MN/Locomotion	7	M2L	0.03001504	Pharyngeal
8	DA05	0.02498552	MN/Locomotion	8	I5	0.02763024	Pharyngeal
9	DD03	0.02392740	MN/Locomotion	9	I2R	0.01609926	Pharyngeal
10	DD02	0.02385313	MN/Locomotion	10	I6	0.01096516	Pharyngeal

It looks like the chemical synapses with the highest stationary distribution belong to 2 communities of motor neurons concerned with locomotion community 1 and pharyngeal neurons community 5.

The 20 neurons listed in the table have the highest stationary distribution in our model. They belong to 2 communities, motor neurons to community 1 and pharyngeal neurons to community 5 (Cook *et al.*). Motor neurons are strongly associated with locomotion in response to sensory stimuli. Pharyngeal neurons act as both sensory but also classify as motor neurons with widespread cross-connectivity that are organized into computational modules that reflect the functional domains of the pharynx in *C. elegans*.

Suggested Reading

[1] Z Chen, S Vijayan, R Barbieri, M A Wilson, E N Brown, Discrete and continuous-time probabilistic models and algorithms for inferring neuronal UP and DOWN states, *Neural Computation*, Vol.21, No.7, pp.1797–1862, 2009.

[2] S Escola, E Fontanini, D Katz and L Paninski, Hidden Markov models for the stimulus-response relationships of multistate neural systems, *Neural Computa-*

tion, Vol.23, No.5, pp.1071–1132, 2011.

[3] H Soula and C C Chow, Stochastic dynamics of a finite-size spiking neural network, *Neural Computation*, Vol.19, No.12, pp.3262–3292, 2007.

[4] S El Boustani and A Destexhe, A master equation formalism for macroscopic modeling of asynchronous irregular activity states, *Neural Computation*, Vol.21, No.1, pp.46–100, 2009.

[5] D H Hubel and T N Wiesel, Receptive fields, binocular interaction and functional architecture in the cat's visual cortex, *Journal of Physiology*, Vol.160, pp.106–154, 1962.

[6] R Yuste, From the neuron doctrine to neural networks, *Nature Reviews Neuroscience*, Vol.16, No.8, pp.487–497, 2015.

[7] R Lorente de Nó, Studies on the structure of the cerebral cortex. II. Continuation of the study of the ammonic system, *Journal für Psychologie und Neurologie*, 1934.

[8] D O Hebb, *The Organization of Behavior: A Neuropsychological Theory*, Psychology Press, 2005.

[9] W Maass, T Natschläger and H Markram, Real-time computing without stable states: A new framework for neural computation based on perturbations, *Neural Computation*, Vol.14, No.11, pp.2531–2560, 2002.

[10] B C Bernhardt, F Fadaie, M Liu, B Caldairou, S Gu, E Jefferies *et al.*, Temporal lobe epilepsy: Hippocampal pathology modulates connectome topology and controllability, *Neurology*, Vol.92, No.19, pp.e2209–e2220, 2019.

[11] M Carboni, M Rubega, G R Iannotti, P De Stefano, G Toscano, S Tourbier *et al.*, The network integration of epileptic activity in relation to surgical outcome, *Clinical Neurophysiology*, Vol.130, No.12, pp.2193–2202, 2019.

[12] S Larivière, A Bernasconi, N Bernasconi and B C Bernhardt, Connectome biomarkers of drug-resistant epilepsy, *Epilepsia*, Vol.62, No.1, pp.6–24, 2021.

[13] S J Hong, B C Bernhardt, R S Gill, N Bernasconi and A Bernasconi, The spectrum of structural and functional network alterations in malformations of cortical development, *Brain*, Vol.140, No.8, pp.2133–2143, 2017.

[14] L Bonilha, J H Jensen, N Baker, J Breedlove, T Nesland, J J Lin *et al.*, The brain connectome as a personalized biomarker of seizure outcomes after temporal lobectomy, *Neurology*, Vol.84, No.18, pp.1846–1853, 2015.

[15] J Royer, B C Bernhardt, S Larivière, E Gleichgerrcht, B J Vorderwülbecke, S Vulliémoz *et al.*, Epilepsy and brain network hubs, *Epilepsia*, Vol.63, pp.537–550, 2022. doi:10.1111/epi.17171

[16] J M Shine and R A Poldrack, Principles of dynamic network reconfiguration across diverse brain states, *NeuroImage*, Vol.180, pp.396–405, 2018.

[17] F V Farahani, W Karwowski and N R Lighthall, Application of graph theory for identifying connectivity patterns in human brain networks: a systematic review, *Frontiers in Neuroscience*, Vol.13, Article No. 585, 2019.

[18] O Sporns, *Networks of the Brain*, MIT Press, 2011.

[19] B C Bernhardt, L Bonilha and D W Gross, Network analysis for a network disorder: The emerging role of graph theory in the study of epilepsy, *Epilepsy & Behavior*, Vol.50, pp.162–170, 2015.

[20] L Dobrunz, Long-term potentiation and the computational synapse, *Proceed-*

ings of the National Academy of Sciences USA, Vol.95, pp.4086–4088, 1998.

[21] S Cioabă and M R Murty, *A First Course in Graph Theory and Combinatorics*, 2nd ed., Texts and Readings in Mathematics 55, Hindustan Book Agency, 2021.

[22] G Grimmett and D Stirzaker, *Probability and Random Processes*, 3rd ed., Oxford University Press, 2001.

[23] G Strang, *Linear Algebra and Its Applications*, 2nd ed., Academic Press, New York, 1980.

[24] R Carter and M. Ram Murty, Some remarks on linear recurrent sequences, in preparation.

[25] S Emmons, Comprehensive analysis of the *C. elegans* connectome reveals novel circuits and functions of previously unstudied neurons, *PLOS Biology*, December 17, 2024. https://doi.org/10.1371/journal.pbio.3002939

[26] M Winding, B D Pedigo, C L Barnes, H G Patsolic, Y Park, T Kazimiers *et al.*, The connectome of an insect brain, *Science*, Vol.379, No.6636, p.eadd9330, 2023.

[27] R Albert and A -L. Barabási, Statistical mechanics of complex networks, *Reviews of Modern Physics*, Vol.74, pp.47–97, 2002.

[28] B Bollobás, Random graphs, 2nd ed., *Cambridge Studies in Advanced Mathematics*, 73, Cambridge University Press, 2001.

[29] G Trensch, R Gutzen, I Blundell, M Denker and A Morrison, Rigorous neural network Simulations: A model substantiation methodology for increasing the correctness of simulation results in the absence of experimental validation data, *Frontiers in Neuroinformatics*, Vol.12, Article No. 81, 2018.

[30] F T Leighton and R L Rivest, Estimating a probability using finite memory, in *Foundations of Computation Theory* (Borgholm, 1983), pp.255–269, Lecture Notes in Computer Science 158, Springer, Berlin, 1983.

[31] V Anantharam and P Tsoucas, A proof of the Markov chain tree theorem, *Statistics & Probability Letters*, Vol.8, No.2, pp.189–192, 1989.

[32] S Vigna, Spectral ranking, *Network Science*, Vol.4, No.4, pp.433–445, 2016.

[33] S J Cook, T A Jarrell, C A Brittin, Y Wang, A E Bloniarz, M A Yakovlev *et al.*, Whole-animal connectomes of both *Caenorhabditis elegans* sexes, *Nature*, Vol.571, No.7763, pp.63–71, 2019. doi:10.1038/s41586-019-1352-7

[34] D R Cox and H D Miller, *The Theory of Stochastic Processes*, Chapman and Hall/CRC, 2001.

[35] S Kim, H Kim, J D Kralik and J Jeong, Vulnerability-based critical neurons, synapses, and pathways in the *Caenorhabditis elegans* connectome, *PLoS Computational Biology*, Vol.12, No.8, p.e1005084, 2016.

[36] S D Larson, P Gleeson and A E X Brown (eds.), Discussion meeting issue "Connectome to behaviour: modelling *C. elegans* at cellular resolution", *Philosophical Transactions of the Royal Society B: Biological Sciences*, Vol.373, No.1758, 2018.

[37] V B Mountcastle, Introduction. Computation in cortical columns, *Cerebral Cortex*, Vol.13, No.1, pp.2–4, 2003.

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