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Identifying the Diffusion Source of Dementia Spreading in Structural Brain Networks

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ABSTRACT

Normal and aberrant cognitive functions are the result of the dynamic interplay between large-scale neural circuits. Describing the nature of these interactions has been a challenging task yet important for neurodegenerative disease evolution. The origin of Alzheimer's disease lies in the hippocampus and subsequently diffuses to the temporal, parietal and prefrontal cortices. Determining the sources of dementia is crucial to the prediction of the disease evolution and choice of treatment. State-of-the-art method for determining dementia progression are network diffusion models derived from the heat equation without diffusion sources. We propose a different research avenue based on epidemic modeling to localize the disease sources. These models may better characterize the empirical spread of dementia through brain regions. We explore an estimation algorithm based on a susceptible-infected (SI) epidemic algorithm and a network diffusion model for comparison purposes emulating the disease evolution from sources (susceptible) to non-recovered (atrophy, infected) areas. The goal is to identify the probable disease diffusion sources, which we accomplish via a ranking heuristic based upon steady-state convergence times. Graph centrality measures are employed to provide a baseline for further comparison. Our results applied on structural brain networks in dementia suggest that epidemic models are able to accurately describe the different node roles in controlling trajectories of brain networks comparably to the existing diffusion approach.

Keywords: Neurodegenerative Disease, Brain Networks, Source Localization, Diffusion, Observer Nodes

1. INTRODUCTION

Understanding the cause and progression of Alzheimer's disease (AD) is one of the most challenging research problems to be solved in the important area of neurodegenerative diseases. Two underlying hypotheses, the amyloid and tau hypotheses, are currently employed when it comes to describe the mechanism of AD. AD induced changes are shown in the functional and structural connectivity of brain networks. Static and more recently dynamic graph theory has been employed to characterize these changes and derive theory-driven biomarkers to be used in disease prediction at the level of the individual subject.

The dynamics of disease progression can be described by diffusion mechanisms taking place on the brain network. There are two main paradigms that could be employed for disease evolution: (1) the heat-diffusion model and (2) the information-centric network paradigm in connection with an epidemic spreading model. Both paradigms comprise the transmission of disease agents (misfolded β-amyloid and τ-protein) over the connectome.

In previous work, the diffusion model was operating without determining the diffusion sources and therefore was insufficient for capturing trajectories of neurodegenerative brain diseases of nonlinear nature.[7–9] A detailed partial differential disease model of stochastic nature was presented in.[2,12,13]

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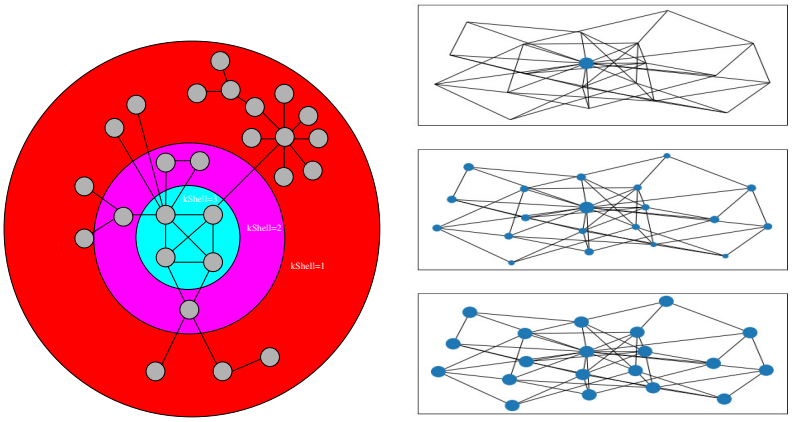


(a) (b)

Figure 1: (a) A schematic representation of a network under the k-shell decomposition.[3] Shells of same degree nodes. Nodes within the core of the network, i.e. with a high k-Shell index, are considered to be good disease spreaders. (b) Convergence of the diffusion model on a random Barabasi-Albert graph to the prescribed $\pi_{diffusion}$ over 1, 10, and 100 iterations. All edges are treated as of equal weight. Node size corresponds to larger $x(v,t)$.

Advanced control theory mechanisms have been a useful tool when applied in connection with graph theoretical techniques to detect brain connectivity and topology changes associated with neurodegenerative diseases. Pinning control mechanisms has been employed to determine the leader or driver nodes that are relevant for disease evolution.[5,10,11]

In this paper, we propose a complex dementia disease evolution system by identifying the diffusion sources[4,14] under the two paradigms of diffusion model and epidemic spreading and determine the diffusion regions for healthy and different stage-dementia subjects in structural brain networks. We employ a heat diffusion model and susceptible-infected (SI) model. We compare these results with brain regions in the structural networks that can act as drivers and move the system (brain) into specific states of action. These influence the cognitive functions. Our results will prove that the experimental neurological findings are confirmed by showing the correct diffusion sources for AD.

2. METHODS

The structural brain connectivity network is described by a graph $G(V,E)$ which has a set of vertices $V = \{v_1, v_2, \cdots, v_N\}$ representing the gray matter structures and a set of edges $E = \{e_1, e_2, \cdots, e_N\}$ describing their connectivity. The disease-causing agent at time t and at each node is given as the vector $\mathbf{x}(t) = \{x(v,t), v \in V\}$. The diffusion model is described by the following "heat equation" model:

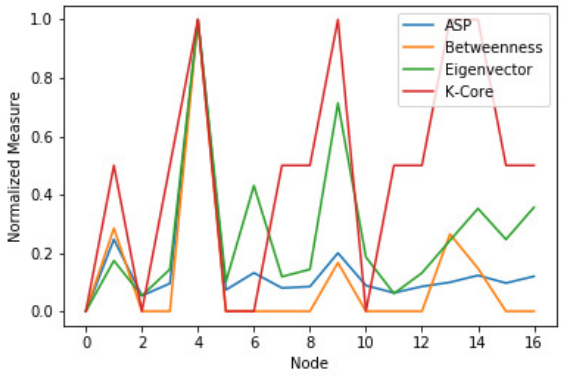
$$\vec{\mathbf{x}}(t_{n+1}) = (I - \beta L^T)\vec{\mathbf{x}}(t_n) + \vec{\mathbf{c}}_{t_{n+1}} \tag{1}$$

with L being the graph Laplacian matrix and I an $N \times N$ identity matrix. The $\vec{\mathbf{c}}$ term allows us to simulate network inflow/outflow or hold the value of some particular v_i constant. $\beta \geq 0$ is a hyperparameter controlling the diffusion speed. Each iteration can be efficiently computed using sparse matrix libraries.

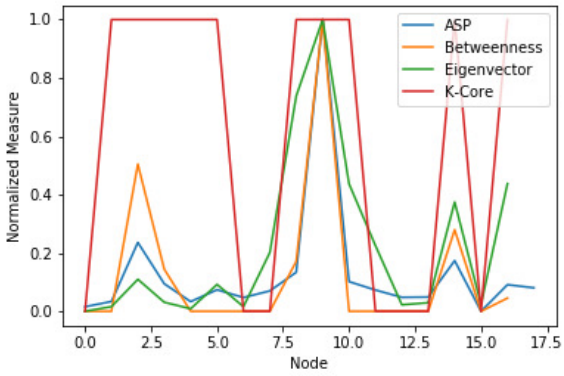
The deterministic SI epidemic model on a weighted graph with normalized adjacency matrix $A \in R^{N\times N}$ and normalized weight matrix $W \in R^{N\times N}$ is described by this equation:

$$\vec{\mathbf{x}}(t_{n+1}) = \vec{\mathbf{x}}(t_n) + \beta(W \circ A)\vec{\mathbf{x}}(t_n) \circ (1 - \vec{\tilde{\mathbf{x}}}(\mathbf{t_n})) \tag{2}$$

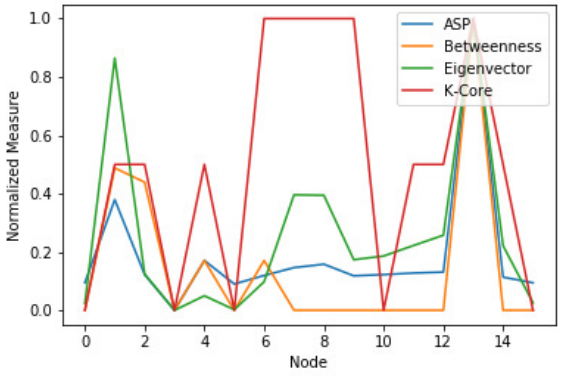
where $\beta > 0$ is the infection rate. We assume A possesses self-loops. It has been shown that the solution of this system when linearized is exponentially stable.[1] In the SI model, the infected nodes of the graph network



(a) Healthy Controls



(b) MCI



(c) AD

Figure 2: Comparison of set of source nodes found based on different graph measures for (a) healthy controls, (b) MCI and (c) AD. Figure adapted from.[6]

represent the disease sources. The stochastic SI epidemic model on the same weighted graph is described by this equation:

$$P(\mathbf{x}(\mathbf{v_i}, \mathbf{t_{n+1}}) = \mathbf{1}|\tilde{\mathbf{x}}(\mathbf{t_n})) = Bern\{\mathbf{x}(\mathbf{v_i}, \mathbf{t_n}) + \beta(\mathbf{1} - \mathbf{x}(\mathbf{v_i}, \mathbf{t_n}))(\mathbf{W} \circ \mathbf{A})_{\mathbf{i},:}\tilde{\mathbf{x}}(\mathbf{t_n})\} \tag{3}$$

with $\mathbf{x}(\mathbf{v}, \mathbf{t})$ now being a binary random variable. The corresponding state space of the deterministic algorithm is used to define a Bernoulli distribution from which we sample $\vec{\mathbf{x}}(v, t_{n+1})$ at each iteration. This algorithm may be accelerated by querying only infected nodes.

It has been shown that the community structure of a network (Fig. 1a) can influence the disease spreading process.[3] In information spreading networks, highly interconnected sub-communities play a key role in this regard. One modality to describe the community structure is the k-core of the network and the corresponding k-shell index of a node in the network. It has to have the highest value k such that the node is still a member of the respective k-core.[3] We compute this and other centrality measures to provide a "naive" node ranking.

To identify the disease sources for both diffusion and SI model, we apply a novel ranking algorithm from the knowledge of the structural brain network. Both models are guaranteed to converge to some stationary distribution π. Given $x(v_i, t) = 1, x(v_j, 0) = 0 \; \forall v_j \neq v_i \in V$, we know *a priori* that $\pi_{diffusion} = 1$ (Fig. 1b) and $\pi_{SI} = 1$. Our approach operates on the following hypothesis: a constant point source placed at an influential node (i.e: nodes which, when infected, are most likely to result in wide disease transmission) will intuitively result in convergence to π in fewer iterations. By recording the convergence rate for all $v \in V$, we are able to construct

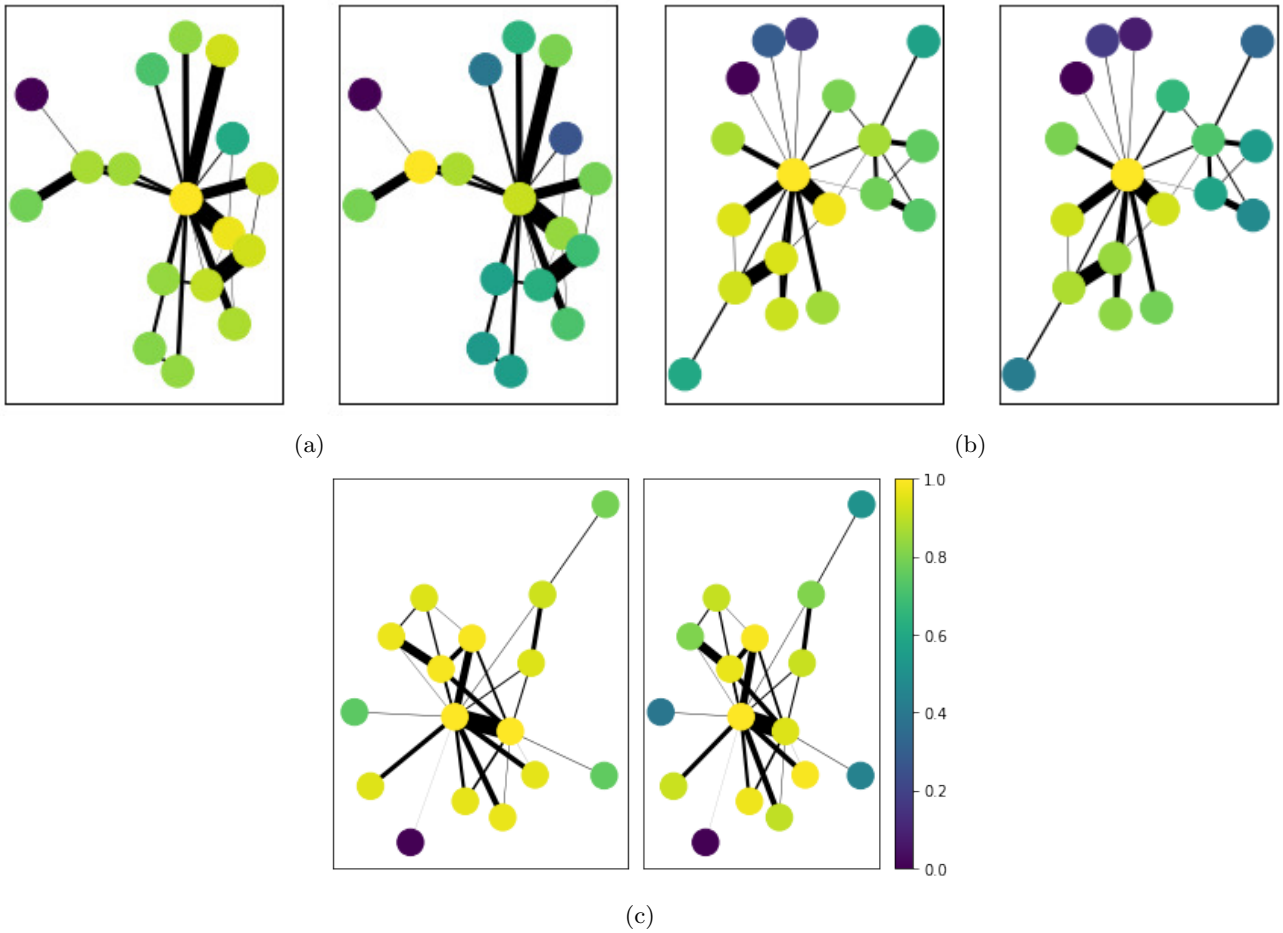


Figure 3: Diffusion (left) and SI (right) normalized convergence times for (a) healthy controls, (b) MCI and (c) AD. Edge thickness corresponds to weight.

a quantitative ranking of each node wherein v_i is considered more influential than v_j iff. the corresponding point source diffuses across the network more efficiently. We employ Pearson correlation coefficient and Kendall's Tau to assess hyperparameter dependencies.

3. RESULTS

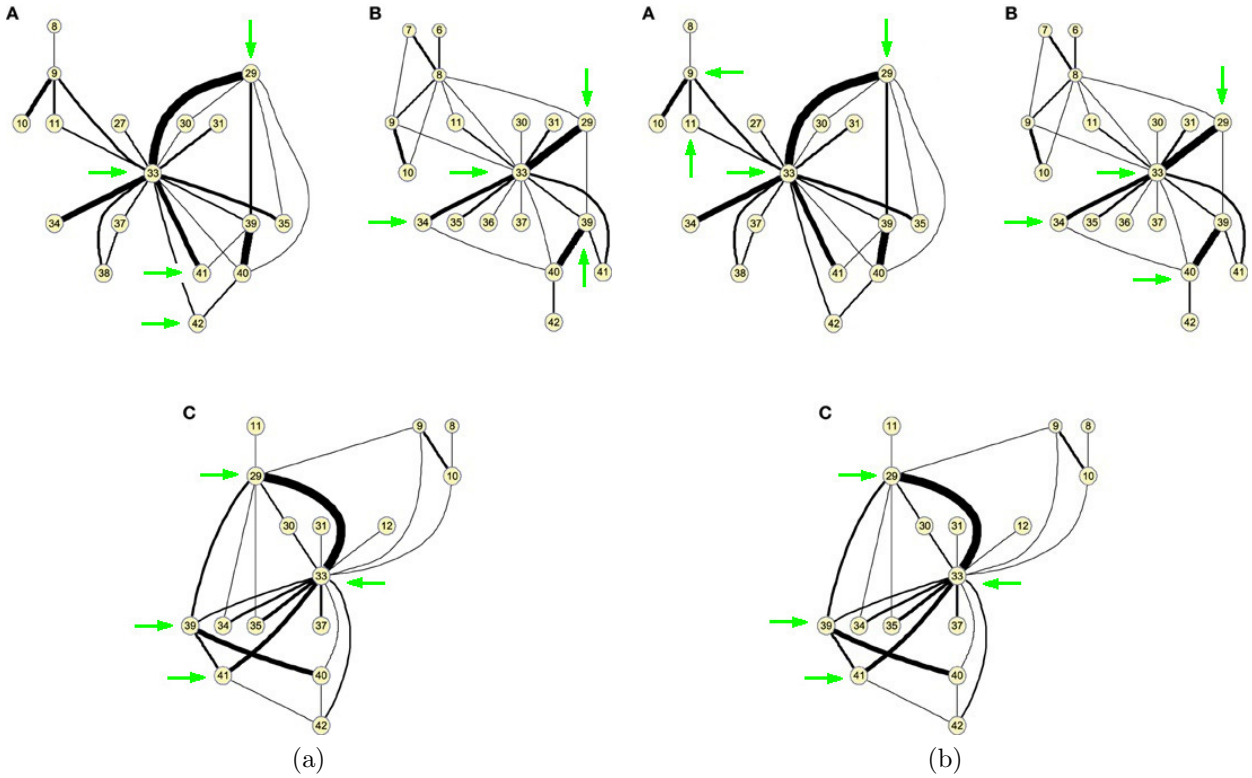
We applied the theoretical models on three structural (MRI) connectivity networks for control (CN), mild cognitive impairment (MCI) and Alzheimer's disease (AD) subjects derived from a subset of the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort in.[6] For the structural data, the connections in the graph show the inter-regional covariation of gray matter volumes in different areas. These networks only consider 42 out of the 116 from the AAL in the frontal, parietal, occipital and temporal lobes. The nodes in the graphs represent the regions while the links show if a connection is existing between these regions or not.

Figure 2 (a)-(c) shows the sources found on the structural data for (A) controls, (B) MCI and (3) AD based on various existing centrality measures.

The source nodes found based on the betweenness centrality measure are fewer for healthy controls with location in the frontal and temporal lobe. There is a shift in the number of source nodes between CN and, MCI and AD. We find an additional node in the hippocampus in MCI and one in the temporal lobe for AD. This confirms the clinical observations that AD originates in the hippocampus. The source nodes for the stochastic SI and diffusion model for CN, MCI and AD are given in the Table 1.

	Healthy Controls	MCI	AD
Diffusion model	29, 33, 41, 42	29, 33, 34, 39	29, 33, 39, 41
Stochastic SI model	9, 11, 29, 33	29, 33, 34, 40	29, 33, 39, 41

Table 1: Nodes representing the top-k sources of diffusion for the stochastic SI model and the diffusion model for CN, MCI and AD subjects. Node IDs refer to the AAL atlas region IDs.



(a) (b)

Figure 4: Comparison of set of source nodes found based on different graph measures for (a) healthy controls, (b) MCI and (c) AD. Node IDs refer to the AAL atlas region IDs.

Table 1 shows that there is a shift of dementia sources (nodes) from the temporal lobe for MCI to the parahippocampal area for AD thus confirming the clinical observations. From Figure 3 (a)-(c), we see that the distribution of convergence times is negatively skewed, particularly for the AD case. This is most pronounced for the diffusion model, whereas SI produces a more even spread in all three subjects. The two models give equivalent top-4 rankings for AD. MCI differs on whether v_{39} or v_{40} occupies the rank-4 position; these nodes are of identical degree and are most strongly connected to each other, so they are naturally similar in rank. In the Control patient, diffusion emphasizes nodes in the 1-neighborhood of v_{33}, $N_1(v_{33})$. SI instead highly ranks the $\{v_9, v_{11}, v_{33}\}$ clique. Figure 4 shows the location of the sources identified in Table 1.

4. CONCLUSIONS

In this paper, we applied a novel ranking algorithm to identify for the first time in literature the sources of disease diffusion in dementia in structural brain networks that are relevant for understanding AD in its evolution. The most important aspect of the algorithm is that it employs the convergence properties of the structural-temporal diffusion dynamics. The algorithm is tested based on two models, the heat diffusion model and the stochastic SI epidemic model. The obtained results confirm clinical findings regarding the origin of AD and its evolution as well as the transition from MCI to AD. The relevance of the proposed method lies in simulating longitudinal studies for dementia cohorts and estimating the probable disease sources from neural connectomes data.

5. CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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