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Modeling Disease Spreading Process Induced by Disease Agent Mobility in Dementia Networks

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ABSTRACT

Dementia progression is based on exploring models predicting longitudinal disease patterns and represents a challenging research field for neurodegenerative diseases. Conventional progression models are mainly continuous network diffusion models assuming a radial contact-based spreading. In dementia-affected brain networks, however, we observe atrophy in specific brain regions that do not assume omni-directional contact-based disease progression but favor a path-based progression relying on misfolded and aggregated proteins flowing from one region to another. Here, we propose a novel concept to biologically model disease progression based on an disease characterization matrix that comprises both the routing and the amount of traversing proteins. We compare the path-based spreading with the contact-based spreading mechanism for brain network graphs for structural MRI data for healthy controls, mild cognitive impairment and Alzheimer's patients. As biomarkers we extract critical epidemic thresholds for both spreading mechanisms. The path-based spreading mechanism corroborates the clinical observations that disease spreading in dementia is persistent and thus increasing the transportation of misfolded and aggregated proteins as with disease evolution will lower the critical epidemic threshold.

Keywords: Dementia, progression, epidemic spreading, brain networks

1. INTRODUCTION

Alzheimer's disease (AD) is one of the most prevalent late life dementia and puts an enormous social and economic burden on our society. Graph theoretical concepts have been for a long time applied in brain research[2, 5, 10, 12] as have been dynamical systems[3, 4, 6, 7, 9] mapped on brain graphs.

The AD disease represents an amyloid-facilitated tauopathy originating in the hippocampus and subsequently advancing to the temporal, parietal and prefrontal cortices. It starts by an accumulation of misfolded and aggregated proteins and progresses along fiber pathways. Morphological and functional changes caused by this pathological progression have been observed on MRI and FDG-PET scans. Progression was shown to favor vulnerable fiber pathways and not neighboring regions. The mechanisms of this networked spread were modeled by predictive network diffusion models as shown in[11] and are not taking into account the above-mentioned problems.

To overcome the modeling challenges of dementia progression, we propose two different network models for dementia progression centered around two different paradigms: (a) contact-based progression vs. (b) path-based progression as shown in Figure 1.

Here we propose to apply epidemic theory to model dementia spread in brain networks. The main aspects of the theoretical framework in analytic epidemiology involve:

1. Disease states: the most common models found are the SIS and SIR.[1] These two models involve as possible states:
   - Susceptible (S): subjects that are not infected yet but prone to infection.
   - Infected (I): subjects that are infected and contagious.

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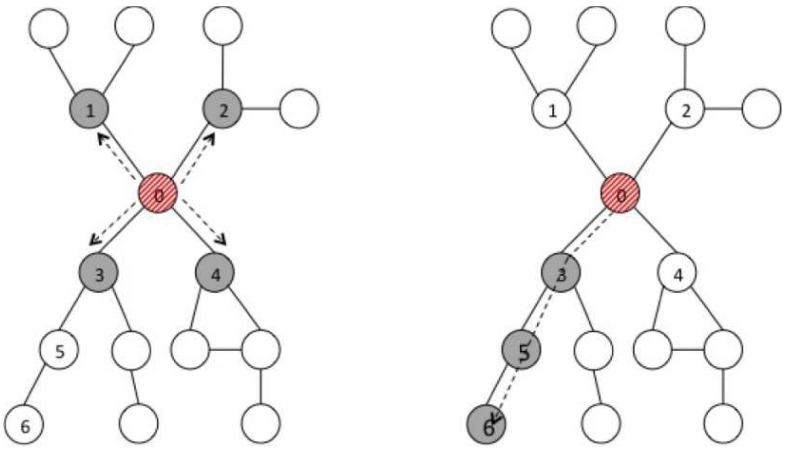

Figure 1. Contact-based vs. path-based in network spread models. Node 0 is the source of atrophy. Grey nodes are susceptible nodes; (left) Contact-based spread of misfolded and aggregated proteins only affect immediate neighbors on all directions; (right) Path-based spread affect all nodes along the probation pathways where misfolded and aggregated proteins traverse and neighbors having no interaction with the affected node are not prone to degeneration. Reprinted from[1] with permission from IEEE.

- Removed (R): subjects that are neither prone to infection or contagious.

2. Infection mechanism: describing how the disease is transmitted from one subject to another. Mathematically this is described by a transition of the states. This is coupled with the effective spreading rate as $\tau = \frac{\beta}{\delta}$ where β is the infection rate and δ is the curing rate.

We consider a continuous-time model for mathematical prediction of disease topography from transneuronal transmission on the brain's connectivity network. The graph-based models are derived from epidemic models and particularly from the class of susceptible-infected-susceptible (SIS) models. We consider an undirected graph network $G(V, E)$ that has a set of vertices $V = \{v_1, v_2, \cdots, v_N\}$ and a set of edges $E = \{e_1, e_2, \cdots, e_L\}$. G is represented by an adjacency matrix A which is a symmetric $N \times N$ matrix.

Every node n at time t in the network has two states: infected or healthy, and at each moment t a node can be only in one of these two states. As proposed in,[1] we denote with $X_n(t)$ the state of the node n at time t and $X_n(t)$ being either "infected" or "susceptible". The probability of a node n being in the infected is state is denoted as $i_n(t) = Pr[X_n(t) = 1]$ and of being in the healthy state is $s_n(t) = Pr[X_n(t) = 0] = 1 - i_n(t)$. By applying directly Markov theory, we obtain an infinistesimal generator $Q_i(t)$ of this two-state Markov chain

$$Q_i(t) = \begin{pmatrix} -q_{1;i} & q_{1;i} \\ q_{2;i} & -q_{2;i} \end{pmatrix}. \tag{1}$$

with $q_{2;i} = \delta$ being the curing rate. The $q_{1;i}$ depends on the propagation model and includes the information about the network topology via the connection matrix A for the contact-based spreading model and about the traffic matrix Γ and routing matrix R for the path-based spreading model. We further assume that both infection rate β and curing rate δ are constant.

There is a critical threshold, the so-called epidemic threshold τ_C, below which the spread of the disease will almost die off and vice versa. For each of the models, there is a specific value.

Currently, there are two mainstream directions regarding infection propagation: the contact-based assuming a radial infection propagation of the same probability and path-based which favors a certain direction. The path-based is overcoming two important limitations of the contact-based: (1) spreading follows certain directions and neighbors are infected with different probabilities, and (2) it takes into account the transportation of an infectious agent.

2. PATH-BASED DEMENTIA PROGRESSION IN COGNITIVE NETWORKS

2.1 Modeling of the Traffic of Misfolded and Aggregated Proteins

There exists traffic from the source and we encode the traffic matrix describing the traffic through the nodes it traverses by the following routing matrix R[1]

$$r_{n,k} = \begin{cases} 1 & : \text{ if the traffic on path k traverses across } n \text{ or is destined to } n \\ 0 & : \text{ otherwise} \end{cases} \tag{2}$$

Besides the matrices A and R, we also define matrix B as the conditional betweenness centrality. The betweenness centrality measures how often each graph node lies on the shortest path between two nodes in the graph. The centrality of a given node u is given as

$$b(u) = \sum_{s,t \neq u} \frac{n_{st}(u)}{2N_{st}} \tag{3}$$

with $n_{st}(u)$ being the number of shortest paths from s to t that go through node u, and N_{st} being the total number of shortest paths from s to t. The nodes are as shown in[1] weighted with their specific traffic generation rate. Let Λ be a $N \times 1$ vector with the entry λ_i representing the traffic generation rate of the nodes in G, then we obtain for the total traffic node n

$$C = \text{diag}(\Lambda) \times B \tag{4}$$

with $diag(\Lambda)$ representing the diagonal matrix. We assume $\lambda_i = 1$ for our applications and that the traffic distribution is uniform. In parlance of epidemiology, we will define C as $N \times N$ disease progression characterization matrix.

2.2 Path-Based Epidemic Threshold

An important parameter in epidemic networks is the so-called epidemic threshold τ_C. It is a critical threshold parameter, theoretically defined as the measure above the epidemics persists.

As shown in,[1] the disease progression dynamics is given as

$$\frac{I(t)}{dt} = (\beta C - \delta 1) I(t) \tag{5}$$

Solving this differential equation we obtain as a result:

$$I(t) = U diag(e^{(\beta \mu_n^C - \delta)t}) U^T I(0) \tag{6}$$

where U represents the orthonormal matrix with the n-th column being the eigenvector associated with the eigenvalue μ_n^C.

Assuming there is insignificant recovery (curing) and we do have mainly disease progression, then the equation from above becomes for $\delta \approx 0$

$$I(t) = U diag(e^{\beta \mu_n^C t}) U^T I(0) \tag{7}$$

For a discontinuing disease progression, the eigenvalues must satisfy

$$\beta \mu_n^C - \delta \leq 0 \tag{8}$$

and this yields for the epidemic threshold the following value

$$\tau_C^{path} = \frac{\beta}{\delta} \leq \frac{1}{\mu_{max}^C} \tag{9}$$

For the epidemics to die off, the epidemic threshold τ_C^{path} is equal or smaller than the inverse spectral radius of matrix C. Thus the disease progression characterization matrix C is the key component of the spreading strength of dementia. μ_{max}^C is the spectral radius of the disease progression characterization matrix C.

3. CONTACT-BASED DEMENTIA PROGRESSION IN COGNITIVE NETWORKS

3.1 Contact-Based Time Evolution of Epidemics

We apply again directly Markov theory and we obtain an infinitesimal generator $Q_i(t)$ of a two-state Markov chain similar to the path-based epidemics as shown in equation (1).

As shown in,[8] the infection dynamics is given as

$$\frac{I(t)}{dt} = (\beta A - \delta 1)I(t) \tag{10}$$

with A being the symmetric adjacency matrix.

3.2 Contact-Based Epidemic Threshold

The time-dependent solution of equation (10) is given as

$$I(t) = (e^{(\beta A - \delta)t})U^T I(0) \tag{11}$$

We use the eigenvalue decomposition $A = U\Lambda U^T$ with $\Lambda = diag\lambda_j$ and $\{\lambda_j\}_{1 \leq j \leq N}$ being the set of eigenvalues of A and U is the orthonormal matrix which has the eigenvectors of A as the columnvectors.

This yields as shown in[8]

$$I(t) = Udiag(e^{(\beta\lambda_j - \delta t)})U^T I(0) \tag{12}$$

Assuming there is insignificant recovery (curing) and we do have mainly disease progression, then the equation from above becomes for $\delta \approx 0$

$$I(t) = Udiag(e^{\beta\lambda_j t})U^T I(0) \tag{13}$$

For a decreasing disease progression, the eigenvalues must satisfy

$$\beta\lambda_j - \delta \leq 0 \tag{14}$$

and this yields for the epidemic threshold the following value

$$\tau_C^{contact} = \frac{\beta}{\delta} \leq \frac{1}{\mu_{max}^A} \tag{15}$$

For the disease to die off, the epidemic threshold $\tau_C^{contact}$ is equal or smaller than the inverse spectral radius of matrix A. $\mu^A max$ is the spectral radius of the adjacency matrix A.

4. RESULTS

We apply the theoretical results for dementia progression based on contact- and path-based spreading on structural (MRI) connectivity graphs for control (CN), mild cognitive impairment (MCI) and Alzheimer's disease (AD) subjects. For the structural data, the connections in the graph show the inter-regional covariation of gray matter volumes in different areas as obtained from MRI data. We considered only 42 out of the 116 from the AAL in the frontal, parietal, occipital and temporal lobes as shown in.[10] The nodes in the graphs represent the regions while the links show if a connection is existing between these regions or not.

The original structural networks are shown in Figure 4.

We determined from Figure 4 the adjacency and infection characterization matrix and computed the corresponding epidemic thresholds and spectral radius for controls, MCI and AD in Tables 1 and 2.

	Contact-based spreading (Adjacency matrix A) $\tau_C^{contact}$	Path-based spreading (Disease progression characterization matrix C) τ_C^{path}
Controls	4.57	4.68
MCI	4.56	5
AD	4.75	3.83

Table 1. Epidemic thresholds for contact- and path-based disease progression in dementia networks.

We see that contact-based disease progression has lower critical thresholds than path-based ones with exception of AD showing that the path-based disease progression dies faster off. This can be explained based on the fact that the contact-based disease progression occurs radially while the path-based relies on the transportation of misfolded and aggregated proteins. Remarkable is that the path-based epidemic threshold for AD is the lowest among controls, MCI and AD. This shows that with the disease evolution as seen with AD, the traffic load of misfolded and aggregated proteins is increasing and at the same time decreasing the critical epidemic threshold.

	Contact-based spreading (Adjacency matrix A) $\mu^A max$	Path-based spreading (Infection characterization matrix C) $\mu^C max$
Controls	0.22	0.21
MCI	0.22	0.20
AD	0.21	0.26

Table 2. Spectral radius for contact- and path-based disease progression in dementia networks.

5. CONCLUSIONS

In this paper, we introduced and compared two disease progression processes in dementia networks, the so-called contact-based and the path-based disease progression. We borrowed the corresponding concepts and terminology from epidemiology and applied them to brain graph networks with particular emphasis on dementia networks. Our results showed that the path-based disease spreading seems to optimally describe the transportation of misfolded and aggregated proteins across brain networks. The standard disease progression model is based on contact-based spreading and modeled by a network heat equation.

We applied the new concepts of path-based epidemic spreading and applied it on structural dementia networks, and thus obtained a biologically plausible explanation of a disease progression model correctly reflecting the increasing traffic load of proteins as AD advances. Our research will contribute towards a better understanding of what the patient's neuroanatomic state will be at any given point in future and unveil the regions that are involved in disease propagation. This will provide new insights about brain organization and brain function, that could not be observed from current studies. This new paradigm will provide us with important disease descriptors showing changes over the disease trajectory such as the hubs of the dynamic system and the weakly

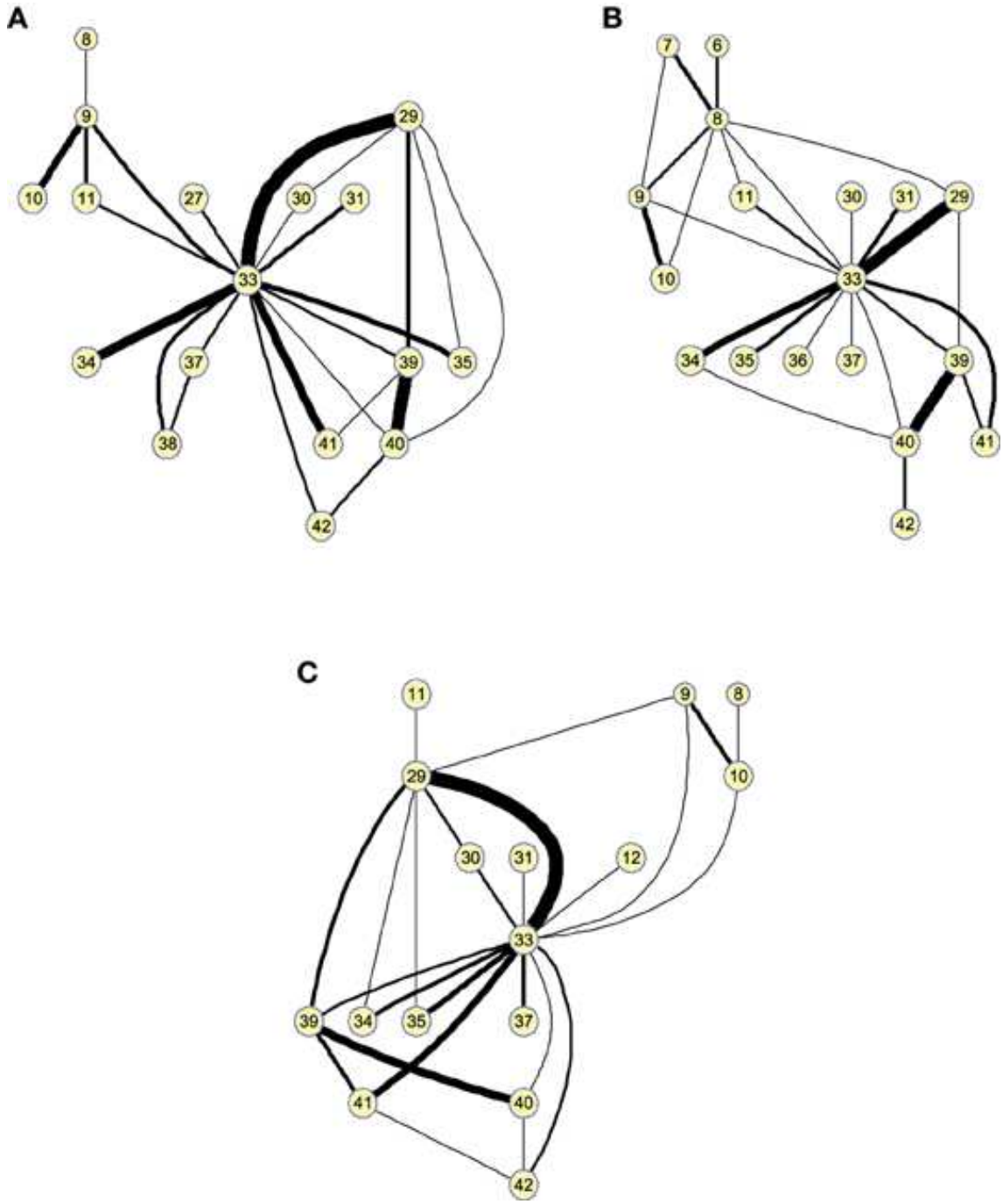

Figure 2. Brain network graphs for structural data for (A) controls, (B) MCI and (C) AD as described in.[10] Reprinted from[10] with permission from Frontiers.

connected areas. Examples are given to elucidate the theoretical results and are in compliance with clinical findings.

6. 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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