Graph Diffusion
Ashish Raj, Phd1, Amy Kuceyeski, PhD2, Michael Weiner, MD2, and Bruce Miller, MD3
1Department of Radiology, Weill Cornell Medical College, New York, NY, United States; 2Department of Radiology, University of California, San Francisco, San Francisco, CA, United States; 3Department of Neurology, University of California, San Francisco, San Francisco, CA, United States

Purpose: Recent studies on prion-like proteopathy[1] of dementias suggest transmission along fiber pathways of the brain network. In a recent paper [2] we modeled the macroscopic consequences of network-centric propagation as a diffusion process on the structural (tractography-derived) brain network. The model accurately recapitulated known patterns of atrophy seen in several dementias. To our knowledge network diffusion constitutes the first fully quantitative, testable model of macroscopic transmission of degenerative processes in the brain. Its neurotic impact arises from its implication that diverse neuropathic etiologies could produce shared spatial patterns whose explanation requires neither selective vulnerability [3] nor focal points of origin [4], nor differential stressor loads [5]. Here we highlight this new advance and put it in the wider context of graph theoretic modeling of dementias. We believe that researchers involved in neuroimaging of neurodegenerative diseases can benefit from a deeper understanding of this exciting new technology.

Outline of content:
A. Overview of diffusion modeling and network-diffusion model of dementia propagation. We will derive how diffusion on the brain’s connectivity network can give a simple model of the dynamics of dementia, as follows. Given the brain’s connectivity matrix (“connectome”) C = (cij), where i and j are node labels corresponding to different structures in the brain. We hypothesize that the regional brain atrophy of diseased subjects, given by the vector x(t) at time t, evolves according to the “network heat equation”\[ \frac{\partial x(i)}{\partial t} = -\beta H x(i) \] where H is the graph Laplacian matrix: \[ H_{ij} = \begin{cases} c_{ij} & \text{for } i = j \\ \sum_{j=1}^{N} c_{ij} & \text{otherwise} \end{cases} \]

Laplacian matrix : \[ H_{ij} = \begin{cases} c_{ij} & \text{for } i = j \\ \sum_{j=1}^{N} c_{ij} & \text{otherwise} \end{cases} \]

exponentiation is \[ x(t) = e^{-\beta t} x_0 \]. Given the eigenvalue decomposition \[ H = \Lambda U \], where \[ U = [u_1, \ldots, u_N] \], we get \[ x(t) = U e^{-\beta t} U^T x_0 = \sum_i \lambda_i e^{-\beta t} u_i x_0 \]. \( \lambda_i \) are eigenvalues of the Laplacian H; the smallest one is 0 and a few are close to 0. Clearly, the eigen-modes \( u_i \) corresponding to large eigenvalues will quickly disappear after a short period of time due to the exponentiation term, leaving only the small eigen-modes, which will persist.

C. Summary of results and predictions. These spatially distinct “persistent eigen-modes” were found to be homologous to atrophy patterns seen in common dementias: normal aging (19 subjects), Alzheimers (AD, 18 subjects) and fronto-temporal dementia (bvFTD, 18 subjects). - Fig 1 taken from [2]. This new advance is a model of the dynamics of dementia, as follows. Given the brain’s connectivity matrix (“connectome”) \( C = (c_{ij}) \), where i and j are node labels corresponding to different structures in the brain. The hypothesis is that the regional brain atrophy of diseased subjects, given by the vector \( x(t) \) at time \( t \), evolves according to the “network heat equation” \[ \frac{\partial x(i)}{\partial t} = -\beta H x(i) \], where \( H \) is the graph Laplacian matrix:

\[ H_{ij} = \begin{cases} c_{ij} & \text{for } i = j \\ \sum_{j=1}^{N} c_{ij} & \text{otherwise} \end{cases} \]

exponentiation is \( x(t) = e^{-\beta t} x_0 \). Given the eigenvalue decomposition \( H = \Lambda U \), where \( U = [u_1, \ldots, u_N] \), we get \( x(t) = U e^{-\beta t} U^T x_0 = \sum_i \lambda_i e^{-\beta t} u_i x_0 \). \( \lambda_i \) are eigenvalues of the Laplacian \( H \); the smallest one is 0 and a few are close to 0. Clearly, the eigen-modes \( u_i \), corresponding to large eigenvalues will quickly disappear after a short period of time due to the exponentiation term, leaving only the small eigen-modes, which will persist.

D. Discussion of implications. These results could explain why degeneration appears to affect distinct and specific sub-networks in the brain [3], as a simple consequence of the brain’s eigenmodes. The model makes specific predictions about the relative prevalence rates of various dementias, which are borne out by published data. Finally, the model can be used to predict future atrophic patterns of any patient using baseline neuroimaging data.

E. Comparison with other related investigations. We highlight some closely related publications [4,6] which used MRI-derived networks to explore the relationship between brain networks and dementia. They conclude that the trans-neuronal transmission model best describes their data, in consonance with our findings. We set this and other papers in the context of neurodegeneration.

F. Finally, we will explore other brain disorders that can benefit from this kind of network dynamic modeling. In particular we will explore epilepsy and Parkinson’s, both of which are considered diseases involving the spread of toxicity in the brain.

Summary: Observed homologies between eigen-modes and dementia atrophy support the hypothesis that all classical dementias might be simply a result of graph dynamics, with various dementias being merely different “eigen-modes” of the diffusion process. This leads to the provocative but plausible idea that neurodegeneration may not have to have a specific focal location, or region-specific predilection. In this presentation we will stress the clinical utility of these network models: that they can predict future atrophy patterns of individual patients from baseline MR scans.


Fig 1: Measured atrophy patterns in AD and bvFTD (top) appears to match well with the 2nd and 3rd eigen-modes of brain network (bottom).

Fig 2: Correlation between measured atrophy and network diffusion eigen-modes. Significant correlations are depicted by green boxes. The association is along the diagonal, implying that there is a one-to-one correspondence between eigen-modes and dementias.

Fig 3: Left: Published relative prevalence rate of various dementias vs. survival time \( 1/\lambda_i \). Right: Published prevalence of AD and bvFTD (dots) as a function of age, along with parameter-optimized model prediction (curves).