STRUCTURAL BRAIN NETWORK AUGMENTATION VIA KIRCHHOFF'S LAWS

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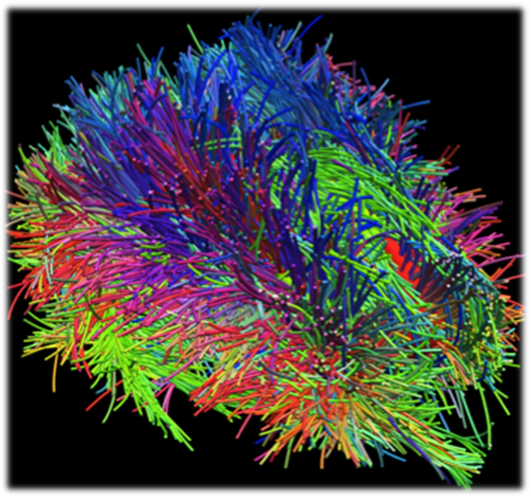
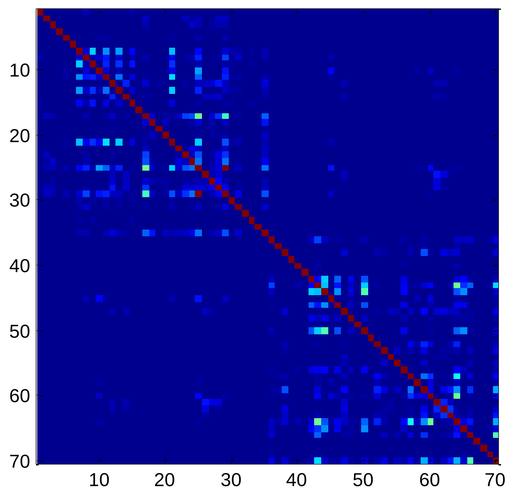
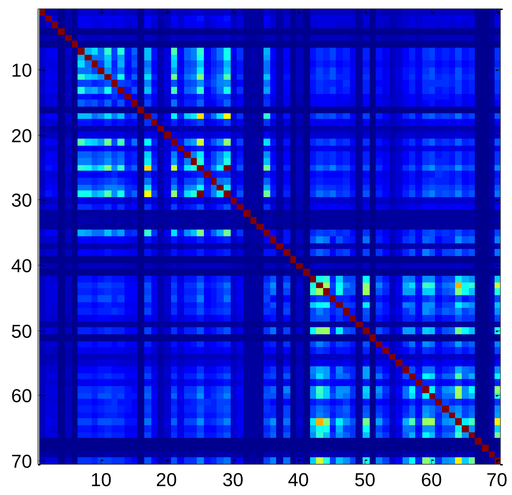


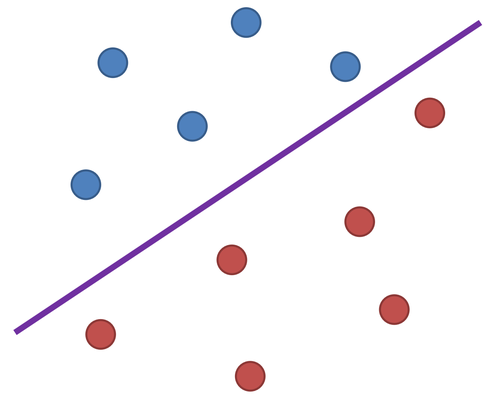
Diffusion MRI tractography



Structural connectivity matrix



Augmented connectivity matrix



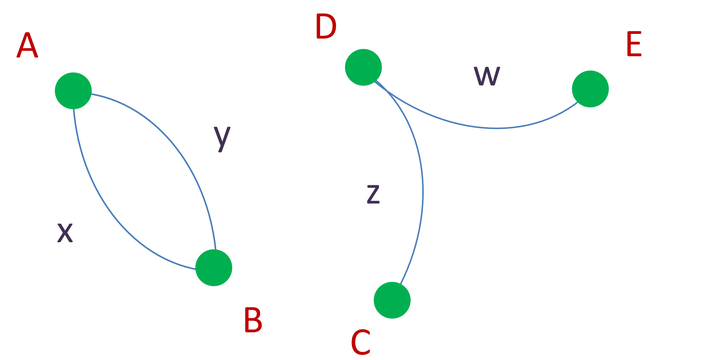
Healthy/disease classification

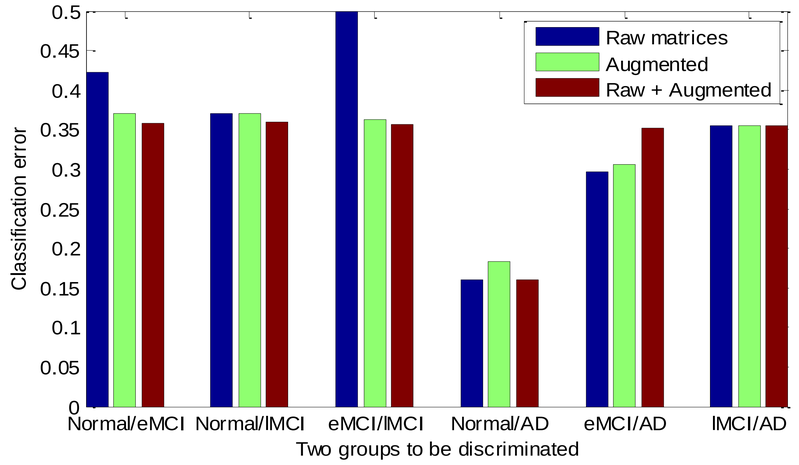
Background: The complete map of connectivity among different brain areas, known as the connectome [1], can be used to study how brain architecture and function are influenced by genetic factors, and change during development and with disease. Standard approaches to compute structural connectivity often define the connection strength between two brain regions based on the tractography streamlines between them. Such a direct fiber bundle is expected to be the major signal carrier between the two brain areas; however, multi-synaptic neural pathways – those relayed through other regions – may also provide connectivity [2–4].

Methods: Here we propose to use the mathematical tools developed for the analysis of resistive electrical circuits (Kirchhoff's circuit laws [5]) to account for indirect multi-synaptic neural pathways, augmenting the information offered by direct brain connectivity, and increasing both the accuracy of connectomic studies and potentially the consistency between structural and functional networks. We model the multiple pathways connecting two regions starting with two simple cases, shown in the graphical figure on the right. *Case 1:* two different fiber bundles connecting regions A and B, with connectivity measures x and y, are considered to have the total connectivity $C_{A,B} \coloneqq x + y$. *Case 2:* indirect connections between the two regions C and E are considered to contribute a total connectivity smaller than each of z and w, as $1/C_{C,E} \coloneqq 1/z + 1/w$. Next, we exploited the similarity of these two basic cases to those of the electrical circuits made solely of resistors, and calculated the total connectivity between pairs of regions similarly to well-developed techniques in electronics (without suggesting that the resistive circuit is an appropriate model for the brain's biological wiring).

Data Processing: Diffusion MR images of 200 subjects from the second phase of the Alzheimer's Disease Neuroimaging Initiative (ADNI-2 [6]), composed of 50 cognitively normal controls, 74 early MCI (eMCI) subjects, 39 late MCI (lMCI) subjects, and 37 Alzheimer's disease (AD) patients, were preprocessed [3], and segmented into 68 cortical regions automatically using FreeSurfer [7]. The orientation distribution functions in constant solid angle [8] were constructed and used as input to the Hough-transform global probabilistic tractography [9], resulting in close to 10,000 fibers per subject. The raw connectivity matrices were calculated, along with the proposed augmented network matrices that account for indirect as well as direct connections. Using the Brain Connectivity Toolbox [1], 35 network measures from each matrix were computed. Support Vector Machines were trained for each type of network (raw, augmented, and both combined) and each pair of groups, and the classification error was computed via leave-one-out cross-validation.

Results: Combining raw and augmented matrices resulted in the best classification among Normal, eMCI, and lMCI (bar plot on the right), suggesting that original and augmented networks contain complementary information. A paired right-tailed Wilcoxon signed rank test revealed significantly smaller Normal/eMCI/lMCI classification error for the proposed (combined) method than the standard (raw) method ($p = 0.005$). For AD vs. Normal and lMCI, the combined network augmentation did not change the results, possibly because direct connections in AD patients are different enough for classification to work well without considering multi-synaptic connections. The eMCI/AD classification is the only one (out of six) where the combined method degraded the results by overfitting.





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