Multi-Modal Structural Networks: Mapping of Connectivity through Diffusion, Functional, and Structural Assessment of Intervening Pathways

J. A. Bogovic[1], M. Chen[1], A. Carass[1], P-L. Bazin[2], D. Pham[2], S. M. Resnick[3], J. L. Prince[1,4], and B. A. Landman[4,5]

[1]Electrical and Computer Engineering, Johns Hopkins University, Baltimore, MD, United States, [2]Radiology, Johns Hopkins University, Baltimore, MD, United States, [3]Laboratory of Personality and Cognition, National Institute on Aging, Baltimore, MD, United States, [4]Biomedical Engineering, Johns Hopkins University, Baltimore, MD, United States, [5]Electrical Engineering, Vanderbilt University, Nashville, TN, United States

Introduction: Mapping connectivity in relation to neurological development, function, plasticity, and disease is widely considered to be one of the most essential challenges for opening new lines of neuroscientific inquiry. Diffusion weighted MRI (DW-MRI) provides the only non-invasive mechanism to assess the intra-voxel structural orientation, and – by inference – local and global structural connectivity [1,2]. DW-MRI derived measures, such as diffusion spectrum imaging (DSI) [2], q-ball [3], and diffusion tensor imaging (DTI) [4], have been proposed as mechanisms to assess structural cortical connectivity through normalized fiber-centric measures between regions of interest. Undoubtedly, DW-MRI provides an incredibly powerful tool with which to assess connectivity, but it is notoriously difficult to validate inference of unknown / abnormal structures. Furthermore, DW-MRI does not directly measure axonal connectivity, and association of DW-MRI metrics with structural connectivity necessitates *ad hoc* interpretation of these measures.

We derive an alternative framework for connectivity analysis, in which structural networks can be inferred with multi-modal characterization of the tissues through which estimated tracts pass. For example, we could characterize the effect of pathology on connectivity could with lesion load and amyloid deposition along white matter tracts between cortical areas. Lesion loads can be robustly quantified with FLAIR imaging (a non-DW-MRI modality), and amyloid deposition measured with PET ^{11}C PiB, so it would seem intuitive to include all available information in the construction of connectivity measures for structural networks. Historically, such analyses have been exceedingly cumbersome and piecemeal due to the lack of support in neuroimaging software to integrate diverse imaging modalities and difficulties associated with visualizing and interpreting results. Our work is aimed at addressing this limitation. We define ***multi-modal structural networks as multivariate graphs to represent connectivity among structural regions***. In these graphs, each edge has a vector-valued weight to represent connectivity through a variety of measures (e.g., diffusion-inferred characteristics: tract length, tract anisotropy, lesion load along tract, or multi-modal assessments: lesion load, quantitative relaxometry, etc.). We present a fully automated system for estimating these multi-modal structural networks and offer these tools for visualizing the intermediate and processed results.

Data: We estimate multi-modal structural networks by combining DW-MRI inferred structure with all available measures of tissue integrity. For this abstract, we present a case study from a healthy, elderly subject (M, 82 y/o) from the Baltimore Longitudinal Study on Aging – NeuroImaging Cohort. This moderate scale, long-term longitudinal study acquires an extensive panel of structural MRI (including MPRAGE, SPGR, FLAIR, dual echo T2, magnetization transfer modalities), DTI, and positron emission tomography (PET: ^{15}O PET to assess cerebral blood flow and ^{11}C PiB to assess amyloid deposition).

Methods and Results: We begin by following [2] in the definition of cortical-centric anatomical regions of interest and using traditional DTI to define connectivity: (1) **Subcortical Nuclei and Cortical Surfaces** are robustly estimated in the presence of lesions by exploiting recent developments in Cortical Surface Using Implicit Surface Estimation (CRUISE) and Lesion-TOpology-preserving Anatomy-Driven Segmentation (TOADS). (2) **Cortical Labels** are determined by non-linear registration of labeled atlases and statistical atlas fusion (with surface Simultaneous Truth And Performance Levelset Estimation, STAPLE). (3) **Traditional DTI** metrics and tracts were distortion corrected and processed with Coregistration And Tensor-estimation a Nicely Automated Package (CATNAP). (4) **Coherent Definitions of Crossing Fiber Bundles** were estimated with Diffusion Oriented Tract Segmentation (DOTS). (5) **^{15}O PET and ^{11}C PiB** imaging were processed and coregistered with structural MRI. (6) **Multi-modal structural networks** are computed with custom software by examining multi-modal contrasts for white matter regions that are identified as connecting labeled regions of interest.

The cortical parcellations form a natural space on which to construct a graph-based analysis. Labeled regions serve as the nodes in the graphical analysis, and edges capture connectivity strength between regions. We infer the paths of structural connectivity with DW-MRI traditional fiber tracking and with DOTS white matter parcellations. Numerous measures of "connectivity" are directly available from the DW-MRI analysis, including statistics on tensor anisotropy, tensor diffusivity, fiber tract length, fiber count, (normalized) volume of white matter parcellations, etc. Furthermore, we exploit coregistered structural and functional (PET) imaging to assess the tissue ***along pathways*** connecting labeled regions. We are able to report statistics for connectivity definitions including amyloid deposition, blood flow measures, and white matter lesion load. Estimated connectivity measures are concatenated into a multivariate structural network graph. All analyses were performed with modules developed as part of the open source Java Image Science Toolkit (JIST). Figure 1 presents an annotated pipeline view showing the fully automated analyses connecting raw data to multivariate structural network graphs. Figure 2 illustrates the intermediate and processed results. The reader is referred to the JIST NITRC wiki for specifics and citations for the indicated methods, a complete binary distribution, and a detailed data processing tutorial [4].

Discussion: We present a fully automated software system using validated and published components to fuse multi-modal information and compute multivariate structural network graphs. These graphs may be used as a natural basis for comparison across subjects and across longitudinal time points that does not necessitate inter-subject or inter-time point voxel-wise registration. Additional analysis modules are available to assess quantitative relaxometry (e.g., T1, T2 mapping) and MT imaging and new techniques can readily be incorporated into the open framework. The multi-modal structural networks can be readily loaded in statistical packages. Certainly, it will be interesting to explore inference with this data structure using larger cohorts, which is now possible given the newly presented software.

References: [1] Y. Iturria-Medina, et al., NeuroImage 36(3):645 (2007). [2] P. Hagmann, et al. PLoS ONE. 7:e597 (2007). [3] M. Perrin, et al. Int. J Biomedical Imaging. #368406 (2008). [4] A. Zalesky and A. Fornito. IEEE TMI. 28(7):1023 (2009). [4] http://www.nitrc.org/plugins/mwiki/index.php/jist:MultiCRUISE

Funding: NIH/NINDS 1R01NS056307 and NIH/NIA N01-AG-3-2124.

Figure 1. Automated JIST Pipeline for Multi-Modal Structural Networks

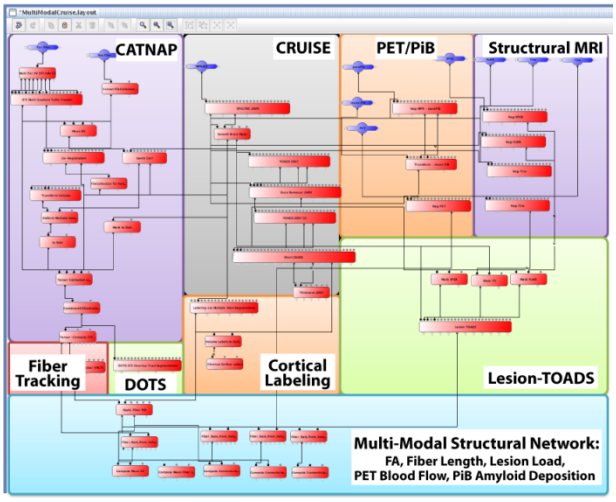

Figure 2. Computing Multi-Modal Structural Networks