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Human Brain Connectomics: Networks, Techniques, and Applications

The human brain is organized into a collection of interacting networks with specialized functions to support various cognitive functions. The word "connectome" first burst on the scene with the work of Sporns et al. [1], who urged brain researchers to advance a comprehensive structural description of the elements and connections forming the human brain. An increasing body of evidence indicates that schizophrenia, multiple sclerosis, and autism exhibit abnormal brain connections. Changes in connectivity also appear to occur as a consequence of neuron degeneration, either from natural aging or diseases such as Alzheimer's disease. A connectome is hence fundamentally important for understanding brain growth, aging, and abnormality. At the micro level, the brain elements consist of single neurons, the amount of which often treads the realm of hundreds of billions, and possible connections between them numbering in the order of 10^{15}. At a more macro (and more manageable) level, the brain is parcellated into a number of regions, where each region accounts for the activity and coactivity of a population of neurons. The colossal task of constructing a connectome calls for powerful tools for handling the vast amount of information given by advanced imaging techniques. In this article, we provide an overview of the fundamental concepts involved, the necessary techniques, and applications to date.

NEUROIMAGING TECHNIQUES

In recent years, emerging magnetic resonance imaging (MRI) techniques with growing sophistication allow deeper insights beyond the brain's gross anatomy to probe functional connections. Functional MRI (fMRI), for example, capitalizes blood flow and oxygen consumption variations within the brain as markers for neuronal activity, and highlights brain circuits that are activated under different stimulated behaviors. Resting state fMRI (R-fMRI), detecting fluctuations in brain activity of a person at rest, can be employed to locate coordinated networks within the brain. High angular resolution diffusion imaging (HARDI) detects water diffusion along fibrous tissue and allows visualization of axonal bundles. The wealth of information provided by these imaging techniques furnishes new opportunities for in vivo investigation into brain circuitry.

THE BRAIN NETWORK

The N regions of a brain form the columns (targets) and rows (sources) of an $N \times N$ connection matrix C that may or may not be symmetric, depending on whether the connection directionality is important. The diagonal of the matrix is often zeroed since self-connectivity is not normally important in this context. The element c_{ij} of C represents connections between individual elements i and j. A confirmed absence of connection is denoted by a zero, while a confirmed presence of connection results in a one. A richer description of the connection is possible by adding physiological parameters, such as connection density, fiber length, and diffusion measurements, as additional layers of information. Combining these pieces of information then allows a structural description of both connection topology and biophysical properties. An illustration of the processes involved in constructing a brain network is given in Figure 1, with the details discussed in the upcoming sections.

BRAIN PARCELLATION

There are apparently a myriad of possible ways for parcellating a brain. There is, however, currently no single universally accepted parcellation scheme for human brain regions. Possibilities range from the commonly used modest 90 anatomically motivated parcellations given by the automatic anatomical labeling scheme [2], to the approximately 1,000 regions of interest defined at the white-gray matter interface used in Hagmann et al.'s work [3]. However, the question of whether structural parcellation of the brain results in functionally distinctive regions is largely unanswered. This is fundamentally important, since understanding brain function in relation to the structural substrate has been a major goal of neuroimaging. Perhaps the most promising approach is what termed as the connectivity-based parcellation, discussed by Behrens et al. in [4], where, based on the observation that functionally distinct gray matter regions manifest different patterns of remote connectivity, the gray matter is parcellated according to its connectional architecture, inferring boundaries between discrete functional regions.

REGISTRATION AND PARCELLATION PROPAGATION

Large-scale comparison of medical images for the purpose of studying brain connectivity cannot yet be performed without first removing confounding intra- or interindividual variations. Factors such as genetics, gender, pathologies, injury, and growth

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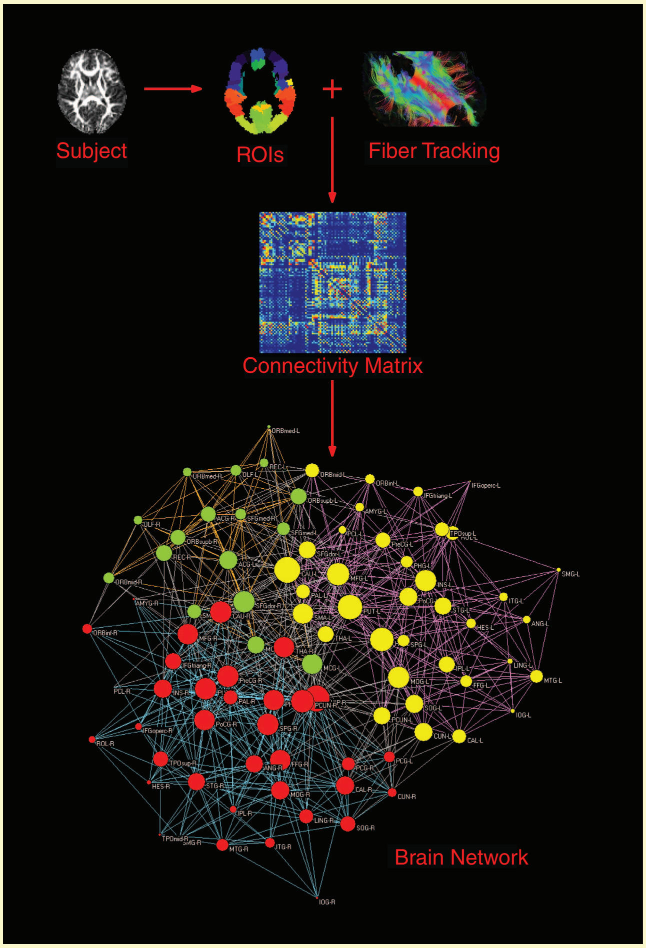

[FIG1] Schematic illustration of the major processes involved in constructing a brain network using fiber tractography. A pair of regions are considered as connected if they are traversed by common fibers, and the numbers of connection fibers are recorded as elements in the connectivity matrix, which is then thresholded to retain only the significant connections. The nodes and intramodular connections are color coded for easier visualization of the communities detected via modularity maximization. The sizes of the vertices are weighted by the (logarithmically scaled) node betweenness.

induce structural variations in the brain. Here, the importance of image preprocessing is therefore to align the population of images into a common space, matching spatially the structures in question. The increased specificity requirement in delineating connection abnormalities or growth related changes place increasing demands on registration algorithms. Thus, for the past two decades, we have seen a flourish of registration algorithms that cater for a wide range of imaging modalities. Upon establishing structural correspondence between a population of brain images and a brain atlas, parcellation information from the altas can be propagated to the individual images for consistent generation of connectivity matrices.

CONSTRUCTING THE CONNECTIVITY MATRIX

Different imaging modalities furnish complementary connectivity information. In what follows, we will discuss how connectivity is defined for some commonly used modalities. Constructing the connectivity matrix involves 1) gathering appropriate features from each region of interest and 2) establishing interregion correlation utilizing the gathered features. Details are as follows.

FEATURES

FUNCTIONAL CONNECTIVITY

FMRI measures the hemodynamic response related to neural activity in the brain and can be used to examine interregional correlation in neuronal variability. Regional functional connectivity is typically estimated using cross correlations, partial correlations, or mutual information of regional time series at one or several specific frequencies. The default mode network (DMN), for example, is characterized by coherent neuronal oscillations at a rate lower than 0.1 Hz.

STRUCTURAL CONNECTIVITY

The cerebral cortex is the outermost layer of neural tissue in the human cerebrum. It plays a key role in memory, attention, perception, thought, language, and consciousness. Connection networks can also be inferred from structural MRI data with brain regional connectivity estimated as correlations in cortical thickness [5] or volume [6]. After parcellating the brain into a number of regions, the mean cortical thickness or gray-matter volume are normally computed for the purpose of estimating the interregion connectivity.

WHITE-MATTER CONNECTIVITY

Diffusion weighted imaging (DWI) has gained considerable interest in the research community owing to its demonstrated capability of allowing in vivo probing of brain white-matter microstructures. In terms of characterizing crossing fibers, HARDI affords more information than the popular diffusion tensor imaging (DTI) and allows superior delineation of the angular microstructure of the brain white matter, making possible multiple-fiber modeling of each voxel for better characterization of brain connectivity. Fiber tractography allows the tracing of fiber bundles defined by the local maxima of the orientation distribution function of each voxel, and a pair of regions traversed by a significant amount of common fibers are considered as connected.

CONNECTIVITY MEASURES

Interregion dependence can be estimated with the help of correlation measures evaluated using fMRI time series, cortical thickness, or gray-matter volume. Pearson's correlation coefficient is commonly used for inferring connectivity from the measured feature values. It is defined as the ratio of the covariance of the two variables X and Y to the product of their standard deviations (σ_X, σ_Y)

$$\rho_{X,Y} = \frac{E[(X-\mu_X)(Y-\mu_Y)]}{\sigma_X \sigma_Y},$$

where μ_X and μ_Y are the means of X and Y, respectively. The computation of the partial correlation coefficient involves an additional step of regressing out the effect of a set of controlling variables, resulting in residuals from which the correlation coefficient can be computed. The controlling variables can include factors such as age, intracranial volume (ICV), or other sources of confounding covariances.

NETWORK ANALYSIS

We provide here formal definitions of some metrics commonly used in the analysis of brain networks. Representing a network as an unweighted graph G with N nodes, its metrics for global efficiency E_{glob} and local efficiency E_{loc} can be computed as

$$E_{\text{glob}} = \frac{1}{N}\sum_{i=1}^{N} E_{\text{glob}}(i),$$

$$E_{\text{glob}}(i) = \frac{1}{N-1}\sum_{\{j:j \neq i \in G\}} \frac{1}{l_{i,j}}$$

$$E_{\text{loc}} = \frac{1}{N}\sum_{i=1}^{N} E_{\text{loc}}(i),$$

$$E_{\text{loc}}(i) = \frac{1}{N_{G_i}(N_{G_i}-1)}\sum_{\{i',j':i' \neq j' \in G_i\}} \frac{1}{l_{i',j'}},$$

where $E_{\text{glob}}(i)$ and $E_{\text{loc}}(i)$ are nodal efficiency metrics, $l_{i,j}$ is the shortest path length between nodes i and j, G_i is a subgraph comprising nodes directly connected to node i, and N_{G_i} is the number of nodes of G_i. Specifically, E_{glob} measures the efficiency of parallel information transfer in the network, whereas E_{loc} measures the efficiency of local information transfer in the immediate neighborhood of each node.

A module of G is a subset of nodes that are more densely connected to each other in the same module than to nodes outsides the module. For a configuration of modular organization m with n_m modules, its modularity $Q(m)$ is defined as

$$Q(m) = \sum_{s=1}^{n_m}\left[\frac{h_s}{H} - \left(\frac{d_s}{2H}\right)^2\right],$$

where H is the total number of edges of G, h_s is the total number of edges in module s, and d_s is the sum of the degrees of the nodes in module s. The modularity of a graph is defined as the largest value of modularity measures associated with all possible configurations of modules, which can be found by optimization algorithms.

Betweenness measures the centrality of a node in a network, and, in some sense, indicates the influence of the node over the spread of information throughout the network. It is calculated as the fraction of shortest paths between node pairs that pass through the node of interest. The betweenness centrality of a node i, is defined as

$$B_c(i) = \sum_{j \neq k \neq i \in G} \frac{\sigma_{j,k}(i)}{\sigma_{j,k}},$$

where $\sigma_{j,k}$ is the number of shortest paths from node j to k, and $\sigma_{j,k}(i)$ is the number of shortest paths that traverse node i.

APPLICATIONS

Recent attempts of utilizing networks as a basis for understanding the brain at a "systems" level have brought new insights into the human brain, demonstrating the fact that a comprehensive description of the architecture of the anatomical connectivity patterns is fundamentally important in cognitive neuroscience and neuropsychology, as it reveals how functional brain states emerge from their underlying structural substrates and provides new mechanistic insights into the association of brain functional deficits with the underlying structural disruption.

SMALL WORLD NETWORKS

Recent research has reached a consensus that the brain manifests small-world topology, which implicates both global and local efficiencies at minimal wiring costs [7]. There are three classes of small-world networks: a) scale-free networks, characterized by a vertex connectivity distribution that decays as a power law; b) broad-scale networks, characterized by a connectivity distribution that has a power law regime followed by a sharp cutoff; and c) single-scale networks, characterized by a connectivity distribution with a fast (Gaussian or exponential) decaying tail. Each network has different degree of resilience to targeted attacks. Studies have also indicated that various neurological diseases, such as Alzheimer's disease [8], schizophrenia [9] and multiple sclerosis [5], cause disruption in the small-worldness nature of the networks. In [8], for instance, the clustering coefficients for the left and right hippocampus were found to be significantly reduced in a Alzheimer's disease group compared to a control group.

CLASSIFICATION AND IDENTIFYING POPULATION DIFFERENCES

Research has moved on to utilize whole-brain connectivity information as the basis for classification and locating population regional differences. In Robinson et al.'s work [10], for example, pattern features were extracted from the connectivity matrices of two age groups (20–30 and 60–90 years) using principal component analysis (PCA) and linear discriminant analysis (LDA). Employing these features for classifying subjects from these two age groups, a K-fold cross validation indicates that a mean accuracy of 87% can be achieved, indicating significant connection changes with aging. In the same framework, they have further identified the key differences between these two age groups.

CONCLUSION

A description of human brain connectome is important for the understanding of brain neurological function, development, and disease mechanism. Effort in this direction can be conducive to diagnosis and the identification of possible biomarkers of neuropsychiatric disorders. This article introduces the fundamental concepts involved in constructing a human brain connectome, commonly used techniques, and some applications to date. The construction of brain connectome will provide a new and exciting venue for the application of signal processing techniques in medical imaging.

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[TABLE 1] WORLDWIDE MEDICAL IMAGING SEMICONDUCTOR REVENUE FORECAST BY PRODUCT.

$M	2006	2007	2008	2009	2010	2011	2012	2013	2014	09–14 CAGR%
DSP	28.8	30.9	31.4	25.8	33.5	39.2	41.2	51	60.6	18.6%

Source: Databeans Estimates

The leading players in the medical ultrasound market, according to Global Industry Analysts, are Aloka Company, B-K Medical, Esaote SPA, GE Healthcare, Hitachi Medical Systems America, Medison Co. Ltd., Philips Healthcare, Siemens Healthcare, SonoSite, TomTec Imaging Systems GmbH, and Toshiba Medical Systems. Philips, Siemens, GE, and Toshiba reportedly account for about 80% of the global market.

The MRI market is projected to reach US$5.5 billion in 2010, driven by the introduction of high-field systems and new techniques such as functional neuro imaging, magnetic resonance angiography, noninvasive colonoscopy, and breast MR.

The key selling point in MRI device selection seems to be its high image quality and cost effectiveness. GE Healthcare, Siemens Medical Solutions, and Philips Medical Systems dominate the global MRI equipment market, according to Global Industry Analysts, while other prominent players include Esaote, Hitachi, Toshiba Medical Systems, Fonar Corp., IMRIS, and Medtronic.

Frost & Sullivan, another research organization that studies the medical imaging market, recently published a report suggesting there is a flurry of research and development (R&D) activity in medical imaging in Europe, particularly for cardiology applications. F&S anticipates a significant market opportunity in the echocardiography segment for manufacturers that can offer portable, PC-based ultrasound systems to private practitioners.

BIG DSP REQUIREMENT

Where does digital signal processing fit into the medical systems market?

Databeans is projecting that revenue from DSPs sold into worldwide medical imaging applications will nearly double from US$31.4 million in 2008 to US$60.6 million in 2014 (see Table 1) as the market for these systems grows and the technology advances on several fronts.

One technical advancement has been the migration of X-rays from film to digital files. DSP is helping convert X-ray signals to digital images at the point of acquisition, with no tradeoffs in image clarity. As TI notes in a report on the future of medical imaging, the ability to render digital images in real-time has led to the use of digital X-ray machines in surgical procedures, enabling doctors to view a precise image during surgery.

MRI is also improving with higher quality images in a fraction of the time required just a few years ago. Also, diffusion MRIs allow researchers to create brain maps to study the relationships between disparate brand regions via tractography. Functional MRIs can now rapidly scan the brain to measure signal changes caused by changing neural activity. DSPs are also playing a key role in telemedicine, particularly in videoconferencing and telepresence systems to support a variety of codecs.

The use of DSP is "a common theme that flows through all of these examples," according to the TI report. More importantly, the technology is having a major impact on healthcare worldwide. [SP]