Tools for tract analysis

Dr James Gee, an imaging scientist working in the realm of big data, is collaborating with John Woo, MD, and Drs Paul Yushkevich and Gary Zhang on a computational analysis framework that can be applied to the study of the brain's white matter. Here, Gee explains their progress so far.

Could you outline your group's background and the work you are currently focusing on?

We are an interdisciplinary team of imaging scientists focused on the problem of how to extract and model information from raw imaging and ancillary data. This information is then used on its own or, more typically, integrated with additional knowledge from complementary modalities; to: characterise a particular disorder; compare different conditions; monitor disease progression or therapeutic response; and, ultimately, aid in diagnosis and prognosis. This work is in the realm of big data science, and expertise in the mathematical, statistical and computational sciences is therefore a prerequisite to everything we do.

How did your group become interested in research on brain white matter?

Diffusion tensor imaging (DTI) had just been developed, and its potential for revolutionising brain white matter studies was immediately evident. At the time, we were already established at the forefront of digital brain atlases and methods for their construction; namely, the ability to take brain images from different individuals and register them together, or spatially normalise them into a common anatomical space. We became involved with the inventor of DTI, Peter Basser, to adapt the registration and spatial transformation technology to this new imaging data type. The developed methods have become the standard in both the acquisition and analysis of diffusion weighted magnetic resonance (DW-MR) images of brain white matter, spearheaded by members of our group. The tract-specific methodology was one such development, which brought to bear separate lines of research within the group on a new approach to studying DTIs of brain white matter. In particular, Dr Paul Yushkevich’s work on object representation and modelling in medical images was, I thought, a natural solution to the problem of analysing white matter tracts in the brain.

What are some of the challenges of studying white matter tracts in imaging studies?

DW-MR imaging is a powerful in vivo imaging technique that allows an unprecedented level of insight into brain connectivity. Despite numerous studies, the field of quantitative diffusion imaging analysis has not fully matured. In particular, the acute interest in fibre tractography – fuelled by its ability to capture connectivity information in diffusion images – hasn’t been completely realised in group studies because of open problems that involve normalisation and quantitative comparison of fibre tracts across individuals. The majority of today’s diffusion imaging studies either employ techniques inspired by voxel-based morphometry or the more recent tract-based spatial statistics approach. These methods have had enormous impact on the field, but neither of them incorporates the connectivity information captured by fibre tractography nor are the inferences gained by these approaches associated with specific brain regions.

How does your tract-specific analysis approach advance the study of brain white matter?

In recent years, there has been an increased interest in statistical brain mapping techniques that are structure-specific. Analysis that takes into account the unique properties of specific anatomical structures can be reasonably expected to have greater statistical specificity, and even sensitivity, than analysis performed point-wise across the whole brain. A key feature of structure-specific analysis is its ability to combine or average data along anatomically meaningful directions while respecting the boundaries between structures – as opposed to uniform smoothing over the whole brain. Furthermore, analysis that restricts its attention to structures of interest produces inferences that can be communicated and visualised more effectively, contextualised by the underlying anatomy. The tract-specific analysis (TSA) methodology provides a statistical analysis framework for DW-MR imaging that is structure-specific and fully leverages the connectivity information encoded in diffusion imagery. The approach uses a surface-based representation to model sheet-like white matter tracts, allowing tract-specific representation, smoothing and statistical inference.

In which direction might TSA progress in the future?

We are excited about facilitating studies that realise TSAs potential for fully exploiting the high-dimensional nature of diffusion imaging data, both to optimally evaluate white matter integrity and to develop population atlases of brain white matter. At the same time, exciting opportunities exist for further methodological advances. The parametric model-based representation of white matter tracts allows the rich collection of statistical tools and visualisation approaches developed in the cortical flat-mapping community to be directly applied in white matter studies. In addition, the rapid progress in fibre tractography and clustering research can be immediately incorporated into TSA to produce higher fidelity models of the white matter tracts in our analyses.
Corticospinal tract impairment in amyotrophic lateral sclerosis.

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THE HUMAN BRAIN is the most complex – and perhaps poorly understood – organ in the body. With a mass of around 1.4 kg, the 100 billion nerve cells contained within are responsible for our every thought, action, memory, emotion and experience. This nervous centre is divided into a number of discrete regions, each responsible for a particular array of our cognitive abilities, and even some of our subconscious actions. Despite this organisation, however, the connectivity between the brain’s neurons is staggeringly complex, with each individual cell able to associate with thousands of others via synapse junctions; connections which adapt and change throughout development as we learn new memories, have novel experiences, and learn additional information.

The brain is made from two types of tissue: grey matter and white matter. Grey matter contains the cell bodies of the neurons and many of the organ’s capillaries – it is mainly concerned with processing and cognition. White matter is mainly composed of myelinated axons of neurons – the long cables that transmit electrical impulses from one region of the brain to the other – and it actively influences learning and memory. Recent advances in imaging technology are making research into the connectivity and activity of the brain more accessible. While electroencephalography (EEG) – first used in 1875 and involves placing electrodes on the scalp to record the electrical activity of the cortex – was once the only method of visualising brain activity, modern approaches such as magnetic resonance imaging (MRI), make use of magnetic fields to provide much more detailed spatial resolution.

A variant of MRI is diffusion tensor imaging (DTI), which allows in vivo analysis of the diffusion of water along the axons of neurons. By tracking these water ‘streams’, scientists can study how different parts of the brain are connected to each other within the vast network of nerve cells. This is a fundamental tool for researchers who are not only trying to gain a deeper understanding of how the brain works, but also those who are investigating the physiological basis of neurodegenerative disorders that arise when brain connections fail. A group of researchers from the University of Pennsylvania (UPenn), led by Drs James Gee and Paul Yushkevich, are working to develop, validate and distribute a statistical analysis framework to improve scientists’ ability to use DTI and fully leverage the connectivity information output by this imaging technique. It is hoped that this can be used to assess how brain connectivity evolves during the normal course of development and is affected by disease.

SOLVING PROBLEMS OF ANALYSIS

Unfortunately, the power of DTI is not yet realised because of difficulties associated with the normalisation and quantitative comparison of nerve fibre tracts across individuals – a problem that the University of Pennsylvania team hopes to solve. The researchers have developed a tract-specific analysis (TSA) framework that draws inspiration from both the curve and skeleton-based approaches that are conventionally applied in the field. The method, as exemplified by the tract-based spatial statistics approach, successfully achieves dimensionality reduction by projecting DTI data onto the skeletons of white matter structures, and uses the most salient geometric features of the fasciculi for analysis of DTI data of white matter. At the same time, the curve-based models are appealing because they provide a way to rigorously establish a coordinate system or parameterisation for each fasciculus of interest in the kinds of neuroimaging studies that are commonly performed. TSA essentially combines the best elements of the curve and skeleton-based approaches.

REAL WORLD VALIDATION

In their recent work, Gee’s team has been working with Dr John Woo to use the disease model of amyotrophic lateral sclerosis (ALS) to validate their TSA framework. This is a

Revealing complex connections

Researchers from the University of Pennsylvania, USA, are trying to demystify brain imaging by developing open source analysis software for scientists investigating brain cell connectivity to work with brain connections in amyotrophic lateral sclerosis (ALS). With the resolution and power of brain imaging techniques rapidly improving, it is becoming increasingly possible to investigate the answers to questions that have long puzzled scientists and physicians about the cause and development of neurodegenerative diseases.
developing TSA in the hope that disorders. "We are continually embracing the international laboratories. The UPenn team is embracing the software has been downloaded of DTI imaging data as well as facilitates spatial normalisation of his PhD thesis at the University of Pennsylvania. "This software provides an explicit description of its own skeleton, which is guaranteed to be a single surface.

The brain connectivity analysis tools that have been developed by the UPenn team have the potential to be used by a broad range of scientists interested in white matter imaging. "It is hoped that our work will enable more effective diagnosis of disease, improve monitoring of the effects of interventions on white matter tracts and answer basic science questions about brain connectivity," Gee concludes.

The progress made by the UPenn researchers is disseminated to the wider DTI research community via the open source and free DTI-TK software package that was developed by Dr Gary Zhang as part of his PhD thesis at the University of Pennsylvania. "This software facilitates spatial normalisation of DTI imaging data as well as the construction of brain atlases, and is among the most popular packages for DTI processing and analysis," highlights Gee. The software has been downloaded tens of thousands of times and is used by numerous high-profile international laboratories.

The researchers hypothesise that ALS has a significant white matter phenotype that can be detected by DTI; imaging can act as a surrogate marker of upper motor neurone integrity to assess the efficacy of experimental therapeutics.

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LOOKING FORWARD
The UPenn team is embracing the opportunity to facilitate the use of DTI analysis in the diagnosis and investigation of neurological disorders. "We are continually developing TSA in the hope that further improvements will increase scientists’ ability to use medical imaging to quantitatively assess the effects of healthy development, ageing and disease on the connectivity between different regions of the human brain," enthuses Gee.

This is an exciting time for neurological study. With the resolution and power of brain imaging techniques rapidly improving, it is becoming increasingly possible to investigate the answers to questions that have long puzzled scientists and physicians about the cause and development of neurodegenerative diseases. Furthermore, the future is looking bright for researchers trying to understand aspects of neural connectivity, which was, until recently, an impenetrable conundrum.

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The TSA framework
TSA is a computational framework for representing the major white matter nerve tracts and analysing the associated DTIs of these tracts. There are four main components:

1) Normalisation – this facilitates the fibre tracking used to identify the tracts of interest, and involves warping all the subjects in a given study to a common ‘atlas’ image that represents an unbiased average of the study subjects.

2) Tract segmentation – the white matter tracts of interest are segmented by fibre tracking, grouping and then labelling.

3) Geometric modelling – a deformable geometric model is fit to each segmented tract. The model provides an explicit description of its own skeleton, which is guaranteed to be a single surface.

4) Statistical analysis – diffusion tensors can be sampled along the direction normal to the model surface and averaged to provide a single value at the skeleton, or, like the popular tract-based spatial statistics approach, the maximum derived DTI quantity of interest can be selected along that projection. The surface-based representation’s unique leverage of fibre orientation in the analysis permits anisotropic smoothing of data where the kernel aperture along and across fibres can be different. A better tradeoff between sensitivity and specificity is therefore possible in TSA through the combination of dimensionality reduction and smoothing on the skeletal surface of its models.