New methodology to quantify biological structures from 2D or 3D images

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Technology description

Background

A growing number of imaging technologies are producing huge volumes of 3D data about biological structures (brain, neurons and blood vessel networks) but the development of analysis tools is lagging behind the technology. Imaging technologies include Computed Tomography (CT), Magnetic Resonance Imaging (MRI), X-ray (for coronary angiography), Optical Coherence Tomography (OCT) in particular OCT-angiography of retinal vessels and capillaries, and Microscope data (confocal, multi-photon, etc).The quantification of biological materials by 3D imaging technologies can provide information that could be used by a doctor to achieve diagnosis of a disease or disorder along with results from clinical tests. Improved analysis methodologies are needed to interpret and quantify this data for diagnosis and management of diseases.

Technology description

ANU researchers have developed novel morphometric analysis methods for emerging types of 3D data images, in particular images from biological specimens. An extension of the method produces accurate models of 3D images of tubular networks such as capillaries or neurons to which the novel segmentation analysis is applied. Data types to which the new methods can be applied include 3D output from microscopy, optical coherence tomography, cardio-angiography, and magnetic resonance imaging. The methods can be applied to brain images or angiography. The methods are extendable to higher dimensional data such as 3D movies (i.e. 4D). The new morphometric methods exploit higher-order, multi-dimensional, spatial correlations in the image data to provide novel measures that have proved to be more informative than conventional measures such as area or volume. The methods are computationally efficient and convenient.

Examples:

Relating brain structure to multiple sclerosis severity

Disease severity in multiple sclerosis (MS) is most commonly quantified using the Expanded Disability Status Scale (EDSS). Disease severity and rate of progression are interrelated. Information to support decisions to change medications is of particular interest, especially given the recent explosion in new treatments for MS. MRI data is the mainstay of diagnosis in MS but unfortunately is relatively poor at assessing disease severity or tendency for progression. To date the MRI variables most related to progression are white and grey-matter volumes. Unfortunately the variance accounted for in EDSS

scores by those volumes is about 10%. While some highly complex models purport to do better they are extremely difficult to validate. The new ANU morphometric measures are based upon higher-order extensions of volume. These relatively simple metrics accounted for more than 25% of EDSS variance in MRI data from 77 MS patients and 30 normal controls. Moreover cross-validated analysis selected the new higher-order measures over volume and other simple measures. In being more correlated with disease severity the new metrics are likely to also be more predictive of MS progression.

Relating retinal capillary structure to age

Retinal capillary health and integrity are critical to eye health. Disturbances of these delicate tubular networks are common in a range of diseases including age-related macular degeneration (AMD) and diabetic retinopathy (DR). The radial peri-papillary capillaries that service the optic nerve head are critical in glaucoma. AMD, DR and glaucoma are the leading causes of visual impairment and blindness. Aging processes are often accelerated in disease, hence ability to quantify capillary age is indicative of power to detect pathology. The ANU researchers investigated the radial peri-papillary capillaries from the retinas of 62 human subjects who ranged in age from 9 to 84 years. The analysis also involved the second part of the patented methods related to forming accurate 3D models of the capillaries from stacks of 2D microscope images or similar data. As with the brain data the new higher-order metrics were consistently selected over simple ones. In particular metrics that quantified the density of loops (collaterals) and the integrated surface curvature were the best determinates of age. Collaterals can help balance oxygen tension, and surface curvature (tortuosity) is related to resistance to blood flow which is known to increase with age. That increase in flow resistance was previously unexplained.

Comparison of retinal vessel data from microscope and OCTa data

Pig retinas are good models of human ones. ANU researchers examined porcine retinal samples using OCT-angiography data from the living retina, and post-mortem microscope stack data as in the previous example. The novel analysis produced remarkably high correlations in the content of the new metrics between OCT and microscope data, and showed that higher-order metrics provided a great deal of information that can be used to distinguish retinal layers.

Neurons

The ANU team examined stacks of 2D microscope data from histologically labelled Retinal Ganglion Cells (RGCs). The nerve fibres (axons) of RGCs form the optic nerve and it is the death of these cells that produces glaucoma. There are about 15 types of RGCs, and the ANU team had data from 46 rat RGCs of 5 types. The patented methods made accurate 3D models of the RGCs and the new morpho-metrics were extracted. The best metrics to classify the RGCs into their types were again the new higher-order metrics. Just 3 of the new metrics allowed 87.0% correct classification. That is, only 6 of the 46 RGCs were misclassified into wrong class out of five possible classes.

Heart arteries

The ANU researchers examined fluoroscopy-based cardio-angiography movie data that were obtained from 3 human hearts. Multiple movies from each heart were examined. Of particular interest were right coronary arteries. The data are 3D in the sense of having 2 spatial dimensions and time. The same 3D modelling and morphometric methods were applied. Again higher-order metrics distinguished the hearts best.
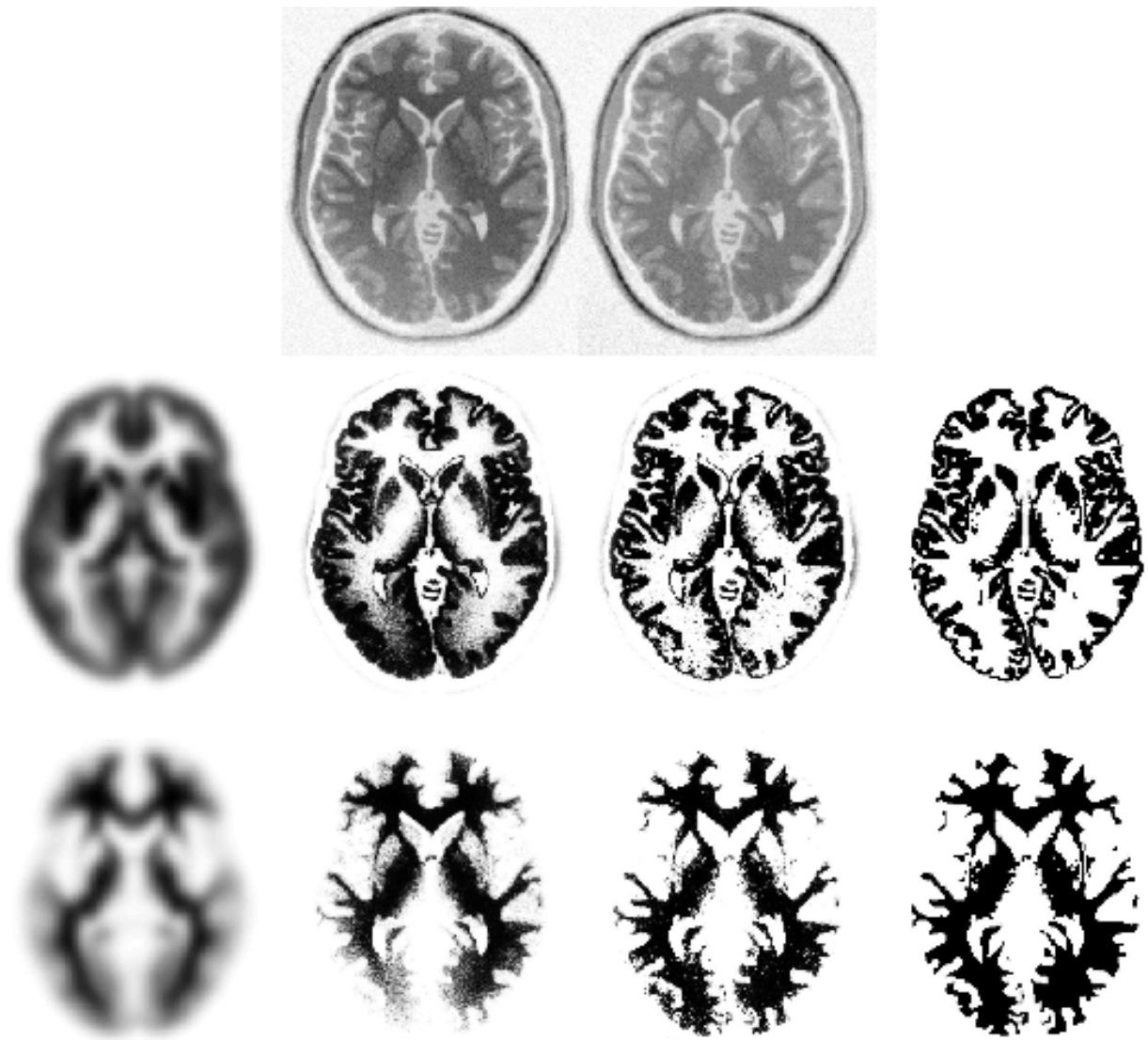
Figure 1. This shows conventional structural MRI data in the top row and then stages in segmenting out grey matter in the middle row (black), and white matter in the bottom row (black). Our new method extracts new metrics from this type of data that are better correlates with severity of Multiple Sclerosis. (Images from Ashbruner & Friston 2004).
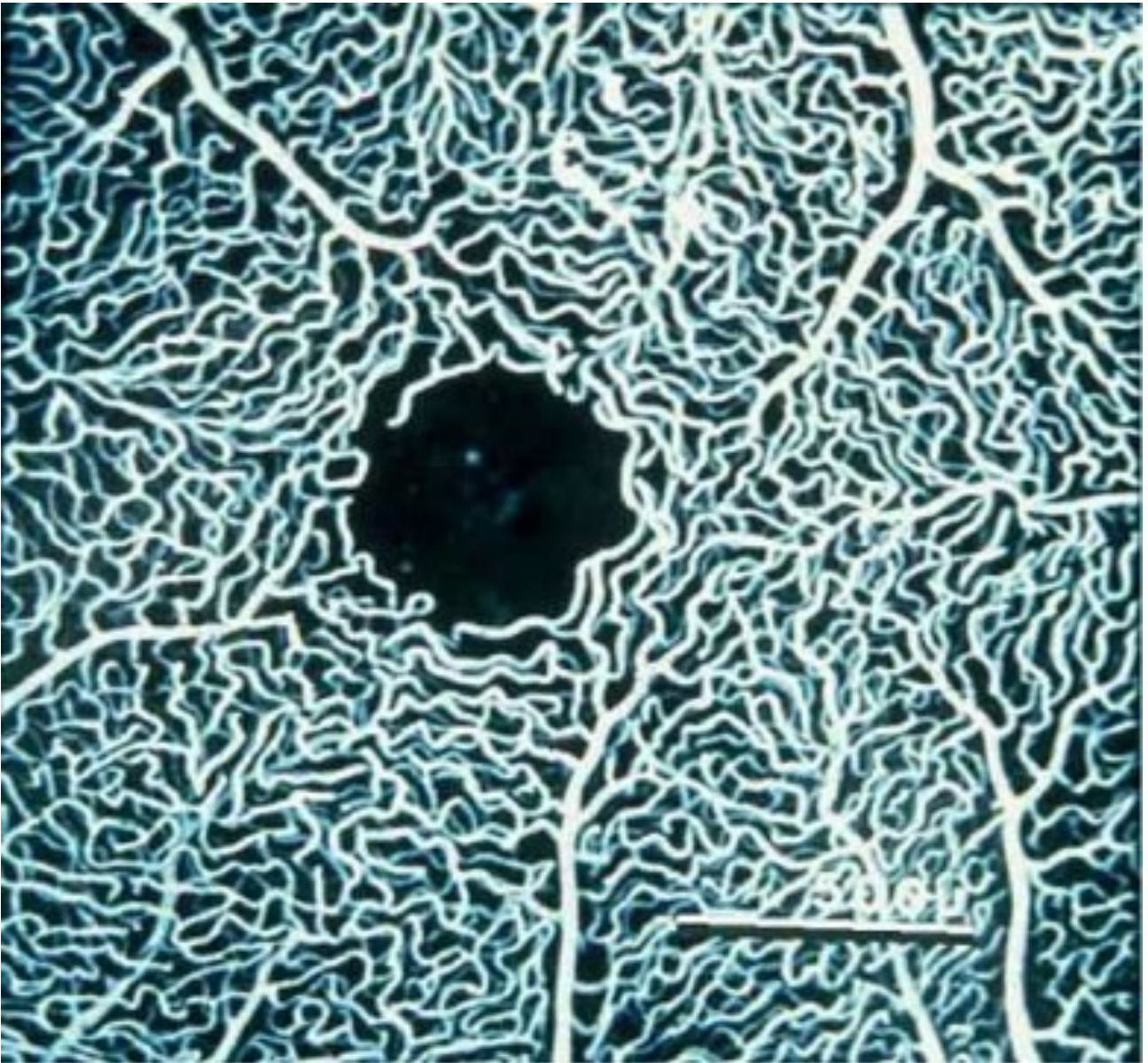
Figure 2. This is an OCT Angiography (OCTA) image of the capillaries of the central fovea, notably showing the central Foveal avascular zone (FAZ). It is the typical presentation of such data as a 2D image. The white pixels label where blood is flowing. The standard measure on OCTA devices is a count of the number of white pixels, that is to say the area of white. The new metrics provide at the very least more information-rich metrics based upon higher-order versions of area. As a second step several 2D images could be fused to an accurate 3D representation to provide even richer 3D metrics.

Application area

Applications include diagnosis and management of a variety of health problems including eye, brain and cardiovascular diseases.

Opthalmology
The global eye examination market is projected to reach USD $3.05 billion by 2022. In 2016 OCT

scanners accounted for the largest share (ca 40%) of the retina and glaucoma examinations product market. This segment is projected to reach USD $882.3 million by 2022 at a compounded growth rate of 9.2% (from 2017-2022).

OCT-angiography (OCTA) has rapidly emerged as a key non-invasive technique for imaging the microvasculature of the retina and choroid. It has significant advantages over established methods in particular the ability to provide "3D" imaging information. OCTA has numerous clinical applications including diagnosis and understanding of many retinal conditions including: diabetic retinopathy, macular degeneration, corioretinopathy, glaucoma and uveitis. Currently only the area of angiography derived pixels is used as the metric for OCTA.

Cardiovascular

Vascular imaging procedures are used for the assessment of blood flow for diagnosis and treatment of various cardiovascular diseases, including fluoroscopy based cardio-angiography. MRI accounted for the largest share (ca 30%) of the global vascular imaging market in 2017 with a market size of USD $1.27 billion and growing at approximately 6.4%; CT an approx. 22% share and market size of USD $0.97 billion; and X-ray an approx. 9% share and market size of USD $0.41 billion Procedures include coronary, peripheral and neurovascular angiography with the coronary angiography segment accounting for the largest share (25%) of the global vascular imaging market in 2017.

Multiple sclerosis

Although the prevalence of MS is relatively low, the early onset of the disease and often the protracted period of disability mean that the resulting costs are high. In Australia alone the costs were $1.75 billion p.a. in 2017. The number and types of disease modifying therapies (DMTs) has increased markedly leading to a 17% cost of since 2010. World-wide costs of DMTs for MS were US$ 19.1 billion in 2016, and are scheduled to increase to US$25.3 billion by 2026. Thus more effective methods for quantifying disease severity and progression are needed.

Brain, neurons

Aside from MS the same techniques could be used to study change in brain morphology associated diabetes, Alzheimers and other diseases. Microscope imaging is improving all the time and a common target for modern imaging is individual neurons.

Advantages

Produces accurate 3D models of the tubular vessel network or similar structures
Enables quantification of the vessel network from the 3D model
Method of quantification is unique and incorporates information related to:
measures of vessel surface area measures of vessel curvature – related to resistance to blood flow, and number of loops which are important in capillary beds and angiogenesis in tumours and macular

degeneration Can also quantify non-tubular 3D data such as brain imaging data including to quantify disease severity in multiple sclerosis

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