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DETECTION OF LONGITUDINAL BRAIN ATROPHY PATTERNS CONSISTENT WITH PROGRESSION TOWARDS ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is the most common form of dementia. In Australia the prevalence of dementia is set to increase from over 400,000 individuals in 2016 to over 1.1 million by 2056. In addition to the rise of individuals with dementia, there is an increase in the associated total annual cost from $8.8 billion in 2016 to $9.1 billion in 2017. These costs include aged care and medical expenses such as hospitalisation, pharmaceuticals and ongoing consultations with health professionals. Due to its social and financial burden, research into AD is a priority in many countries, including Australia. Once the pathology of AD is better understood, preventative measures, early detection and therapeutic treatment of the disease can be better managed.

Progression along the AD syndrome has been accurately monitored with neuroimaging technology such as structural magnetic resonance imaging (MRI). Recent advances in structural MRI have enabled the detection of minute brain tissue measurements on presymptomatic individuals prior to cognitive decline due to AD onset. Statistical models, which take into account the structure of MRI data over time, have provided vital insight into the complex properties of morphological brain patterns that are unique to AD.

Typically, structural MRI models at the region of interest (ROI) level focus on either biological models on a single region over time or on the organisation of multiple ROIs through covariance networks. While both approaches complement each other in terms of neurodegeneration modelling, when analysed independently they provide an

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incomplete picture of the underlying process. Furthermore, approaches that consider models on ROIs over time place restrictive assumptions on how the regions co-vary. A final limitation of current approaches is that they do not lend themselves to incorporating external information before or after model estimation. This limits the ability to address a wider scope of research questions beyond the information provided from the data at hand.

This research aims to develop and apply statistical approaches to combine morphological ROI models with covariance network structures. The intended application of these models is to provide clinical insight into the detection of longitudinal brain atrophy patterns consistent with progression towards healthy ageing or AD.

This thesis progressively develops Bayesian hierarchical models to take into account the spatio-temporal nature of the data while providing morphological region and covariance network estimates. The aim of this research is broken down into four objectives. The first two objectives consist of longitudinal analyses independently applied to two key AD brain regions, and an efficient method is proposed to estimate the covariance structure of several ROIs. The third objective combines the methodology from objectives one and two in a hierarchical Bayesian framework to jointly model ROI morphological features and the covariance network of the brain. A final extension to the model from objective three facilitates the estimation of change in brain networks over time while taking into account the uncertainty of all possible connections.

In the first objective, three important clinical research questions were answered by the application of a Bayesian hierarchical model on two ROIs [1]. The addition of prevalence rate information to our model results was used to estimate probabilistic trajectories over age on healthy, mild cognitive impaired (MCI) and AD groups, and identified critical time points where healthy ageing and AD begin to diverge. The second objective was achieved by the estimation of a connectivity structure through maximising the network likelihood (MNL) [2]. The proposed method showed superior performance against a state-of-the-art alternative in both simulation and applied case study scenarios. The MNL approach formed the foundation for future network estimation in this thesis. The third objective combined the methodologies of the first and second objectives through the estimation of wombling models in a Bayesian hierarchical framework [3]. On structural MRI data, the wombling model facilitates a joint analysis of ROI thickness estimation contingent on probabilistic connectivity networks, determined by the covariance structure of the data. Cortical covariance networks from the wombling model were found to decrease in connectivity from healthy to MCI to AD, and the cortex progressively declined along the dementia pathway. The last objective extended the methodology from objective three to develop the dynamic wombling model, which characterises changes in network configurations along a continuous age domain [4]. On healthy and AD groups, the dynamic wombling model identified connections, which differed quickly or slowly over the age range of 55 to 95 years, as well as steady connections, which did not vary over age.

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Cortical thickness estimates at the participant and population level showed discernible differences between healthy and AD groups, including regions with little or no connections.

This thesis presents four statistical approaches to address complex neurodegeneration modelling on a range of data structures, such as single or multiple sets of ROI observations, as well as on cross-sectional or longitudinal data. The work presented in this research will extend our ability to estimate ROI morphological changes and connectivity structures to better understand ROI differences over age and along the AD pathway. This will allow practitioners to model ROI information at a global and participant level, and identify key points in time when brain connections change.

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