UNIVERSITY COLLEGE LONDON

MRES PROJECT PLAN

Differential Diagnosis of Alzheimer subtypes using disease progression modelling

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Aims of the project

We are planning on modelling PCA using an *event-based model* (EBM), which models the progression of the disease as a sequence of events, where each event corresponds to a biomarker becoming abnormal. The biomarker dataset is multimodal and includes measurements of atrophy rates of cortical volumes, cognitive test scores and presence of proteins such as Amyloid beta.

Project Background

Dementia and other related neurodegenerative disorders cost the UK approximately £26 billion a year. Developing a clear understanding of how these disorders operate and progress over time could help us find more effective treatment. This project is investigating the progression of Posterior Cortical Atrophy (PCA), which is an early onset variant of Alzheimer's disease that causes atrophy of the posterior part of the cerebral cortex, resulting in disruption of the visual and motor systems.

Symptoms include blurred vision, impaired ability to read, difficulty with depth perception and navigating through space. The cause of PCA is still unknown and there are no fully accepted diagnostic criteria. PCA patients are often misdiagnosed with anxiety disorder or depression. Moreover, no specific and accepted scientific treatment for PCA has been found so far due to the rarity and variation of the disease. All these factors together show that more research into PCA is needed and the EBM can assist to this. It could lead to better understanding of PCA progression, and can be used as a clinical tool for prognoses and differential diagnosis.

Motivation

The EBM has already been used to study familiar and sporadic Alzheimer's disease and Huntington's disease (HM Fonteijn et al, 2012, Young et al 2014).This project aims to apply these techniques in the study of PCA. We will be interested to find the most common event progression, use it to classify patients into several groups according to their disease stage. We will also do some longitudinal studies, such as finding the probability of a patient converting from cognitively normal to mild cognitive impairment or from mild cognitive impairment to PCA over time. The EBM would be very useful as a clinical tool because it can provide prognostic information regarding the progression of PCA. It could also be used to perform differential diagnosis, which is the aim of the project.

List of tasks — Deadline

Data collection and preprocessing — 10 April

One needs to run segmentation algorithms to compute atrophy rates from MRI images of PCA patients. Data also needs to be collected and processed for other types of biomarker measurements, such as cognitive test scores and blood tests.

Implement the EBM — 24 April

One needs to read about the EBM and design the PCA-based EBM. The choice of distributions modelling the subject measurements might be different from previous EBM implementations.

Initial results: — 8 May

Use the EBM implementation to get some initial results for PCA: positional variance matrices and stage histograms for different groups.

Analyse follow-up data — 15 May

Analyse follow-up data and compute plots showing longitudinal consistency of patient disease stage. Also fit Cox proportional hazards models to find the probability of patients of converting from cognitively normal (CN) to mild cognitive impairment (MCI) or from MCI to PCA over time.

Build disease stage classifier — 29 May

Build a simple classifier using cut points in the histogram data which would be able to classify patients in the three main categories: CN, MCI and PCA.

Differential Diagnosis of PCA vs other AD subtypes — 19 June

Use the EBM to perform differential diagnosis of PCA and other Alzheimer's subtypes.

Validation of the results — 3 July

Compare the results of the PCA-based EBM with other disease progression methods, such as those based on differential equations or self-modelling regression approaches.

Simultaneous MCMC sampling — 20 July

Implement MCMC sampling of both the model parameters and the most probable disease progression. This feature has not been tried in previous EBM implementations.

Write the MRes project report — 14 August

Write the MRes project report showing all the results obtained so far.

Summary of progress to date

I have so far experimented with the EBM by trying to reproduce some of the results of A. Young, 2012. We managed to get the MRI images from the Dementia Research Center. We are still missing the data from protein biomarkers and cognitive test scores.