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Biometris
Quantitative methods brought to life

Detecting ApoE4 with plasma metabolites

a Machine Learning approach

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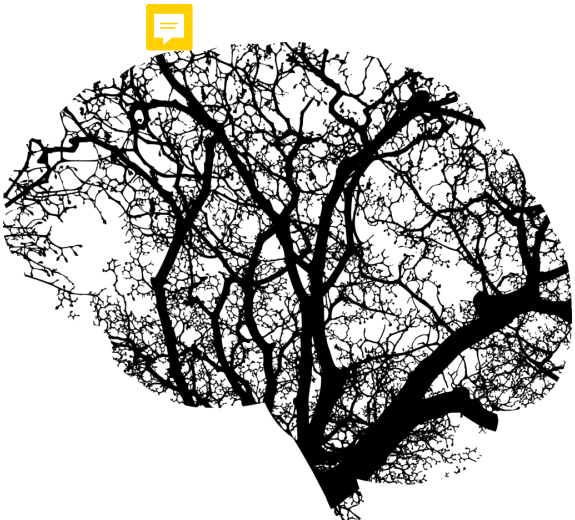

Contents

1. Introduction

1.1. **Background.** Alzheimer's Disease is a progressive neurodegenerative disorder and the most prevalent form of dementia [1]. One person is diagnosed with Alzheimer's every 3 seconds, with a two-fold increase in incidence every 10 years i.e., 10% at the age of 65, 20% at 75, and 40% at 85[2]. The impact Alzheimer's has on patients, their caregivers, and health systems is detrimental. In fact, it has an estimated annual global societal cost that exceeds the GDP of The Netherlands [3].

The disease course begins with an asymptomatic phase of approximately 20 years, during which neurons are damaged [4]. It is followed by an early symptomatic phase, marked by an emerging cognitive decline. Chronic neuroinflammation leads to protein misfolding and sedimentation in the brain over time, mainly amyloid-β ($A\beta_{42}$, $A\beta_{40}$) and hyperphosphorylated tau [5]. To date, there is no disease modifying treatment for Alzheimer's.

An early diagnosis can still be beneficial for individuals and their close ones [6]. Detecting Alzheimer's early enables individuals to understand their condition, actively participate in healthcare decisions and use treatments more effectively. An early diagnosis allows patients to prioritise their goals, make informed legal, financial, and care decisions and access supportive resources from relevant organisations. Having a better understanding of the disease, families can provide more effective support, while those diagnosed can contribute to research by participating in clinical trials. Moreover, sharing first-hand experiences can raise awareness, help reduce the stigma surrounding dementia and encourage others to seek support [7].

The diagnostic algorithm for Alzheimer's traditionally involves the assessment of cognitive functions, behavioural and psychological symptoms through clinical examination and standardised questionnaires [8]. However, growing research is underway to support the diagnosis and progression of Alzheimer's with biomarkers[4], [9]–[12].

Structural and functional neuro-imaging techniques such as magnetic resonance imaging (MRI and fMRI) and positron emission tomography (PET) scans are routinely performed in the context of Alzheimer's diagnosis [8]. These techniques are based on measuring the shrinkage of specific brain areas. However, a recent systematic review recommends the use of structural MRI to rule out nondegenerative or surgical origins of the cognitive decline, rather than diagnosing Alzheimer's-induced dementia [13]. Moreover, in clinical settings, it is not advised to rely on brain area volumes calculated by structural MRI for early detection of Alzheimer's-related dementia[13].

Advances in computational power, AI and particularly in Deep Learning (DL) led to several models being released that detect signs of Alzheimer's in MRI and PET images, even at early stages, with almost perfect testing accuracies [14], [15]. Nonetheless, a systematic review revealed that most of the MRI-based models are trained on the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu), which implies population overlap [16]. Furthermore, another review identified several challenges in the implementation of Convolutional Neural Networks trained on 3D neuroimages for the diagnosis of AD, i.e., data leakage problem (information from the test set leaks into the training set), overfitting (the model learns the intrinsic particularities of the training data, capturing noise and irrelevant patterns, leading to poor performance on new, unseen data) [17]. A large amount of neuroimaging data is needed to train these models, in service of improving their performance on new patient data. Early Alzheimer's might not be detectable by neuroimaging [8], but molecular disturbances could still be detectable with analytical methods.

On the molecular front, -invasive- Cerebrospinal fluid (CSF) aspirations are used to detect Alzheimer's and support its diagnosis. High levels of $A\beta$ and tau proteins in CSF usually serve as confirmation of Alzheimer's diagnosis [18]. Nevertheless, given the risk of lumbar punctures, research is focusing on peripheral blood metabolites as functional intermediate phenotypes[12], [18]–[24].

Metabolites are rigorously studied as biomarkers or targets for treatment [25]. Lipid metabolism is of particular interest [19], [26], [27]. The Apo-lipoprotein-E-4 (ApoE4) allele is the main genetic risk factor for Alzheimer's[27]–[33], as 50% of the patients have at least one copy of the gene[31]. ApoE4 mediates the onset and epidemiology of Alzheimer's Disease[31] by promoting $A\beta$ plaque formation, tau

misfolding, microglia and astrocyte activation, associated neuroinflammation and neurodegeneration[28]. Other metabolites associated with Alzheimer's Disease are amines, aminoacids[18], [34], cholesteryl esters [19], sphingolipids [25], [26], [34]–[36], fatty acids[18], [27], glycerophospholipids[20], [35], [37], [38], phosphatidylcholines [39] and lipid peroxidation compounds [27].

These molecules are usually identified via high-throughput metabolomic pipelines (coupled with Mass Spectrometry or Nuclear Magnetic Resonance) that trace all metabolites in a sample and result in high-dimensional data [40]. The latter often require machine learning, dimension reduction techniques, e.g. projection to latent structures [20] or (covariance) network analysis using graphical models [18] in order to extract putatively meaningful information. Leeuw, Peeters, Kester, *et al.* discovered distinct metabolic signatures among Alzheimer's patients and controls, with differences in their cohesion depending if they had the ApoE4 allele. Therefore, it could be insightful to assess the performance of a metabolomics panel in predicting the ApoE4 genotype.

1.2. **Research Questions.** Spinal cord aspirations are risky and invasive. It is, therefor, of great scientific and societal interest if statistical models trained on (peripheral) plasma metabolites can reliably discriminate between pathologic ApoE4 genotypes and healthy ones, regarding to Alzheimer's.

RQ1: ~~How accurately can plasma metabolites be used predict the ApoE4 genotype~~?

RQ2: How does projection latent orthogonal structures affect the performance of the metabolite classification models?

2. Approach

The data come from the Amsterdam Dementia Cohort [18], [41] and contain 230 metabolites and oxidative stress compounds. The data were collected from Alzheimer's disease patients with or without the ApoE4 allele. In the proposed research, the data will be processed and transformed appropriately to facilitate model fitting. All analysis will be performed in R, with packages such as rags2ridges [42]. The final Thesis report will be written in LaTeX, as is the current proposal.

It is of interest in this project to find the optimal balance between model performance and interpretability. Interpretable models such as (L1, L2 and mix L1/L2 penalised) Logistic Regression, Decision Trees, shallow Artificial Neural Networks often fail to discriminate as well as Random Forests or other blackbox models. The classification performance of the aforementioned models will be assessed using the AUC (Area Under the ROC curve) and other metrics such as Accuracy, Precision, Recall and F1-score.

The data will also be projected to Latent Orthogonal Structures using the FMradio package [43]. The Maximum Likelihood (ML) Factor Analysis will filter out redundant features while maintaining the variance in the data. The resulting matrix will contain less features and will then be fitted in the aforementioned models and their performance will be evaluated with the same metrics.

FAIR Principles. The FAIR Guiding Principles for scientific data management and stewardship were published by Wilkinson, Dumontier, Aalbersberg, *et al.*in 2016. FAIR stands for Findable, Accessible, Interactive, and Reusable data; the intention is to create and use data that well-documented and reproducible. These principles will be considered at every step of the proposed project and implemented if applicable. In practical terms, this could mean creating a publicly accessible git repository to pull the code, documentation and author contact information.

3. Risk Assessment

4. Scientific and Societal Impact

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