Abstract

The student will employ AI methods to find weak signals in Raman spectroscopy, to improve the diagnostic accuracy for neurodegenerative diseases, and apply to urine and blood samples acquired from patients with various neurodegenerative diseases to integrate data into a single test. Time-based studies on individual patients will be conducted to monitor a patient's condition during treatment.

Introduction

850,000 people in the UK live with neurodegenerative diseases. Costs of dementia in the UK (NHS, social care and unpaid care costs) were estimated at £34.7billion in 2019 [1], and £94.1billion in 2040. Early, accurate diagnosis allows for earlier patient intervention and reduced cost, notably with therapeutics which slow the rate of progression [2].

Diagnosis depends on type of disease, including genetic and other biomarkers [3], as well as behavioural tests, imaging and pathology. Accuracies vary by disease, from 70-95%. Distinguishing diseases and variants can be difficult [4], so a single accurate test for multiple diseases would revolutionise diagnosis. We propose such a screening test using urine and/or blood plasma, with low false positive rates required for multiple diseases.

Raman spectroscopy uses a laser to excite vibrations within molecules [5]. A photon loses energy when exciting a vibration, and by detecting scattered photons with a spectrometer we can deduce the vibrational frequency and therefore type of bond excited within the molecule. Biological tissues contain complex mixtures of biomolecules, and subtle differences in chemical composition caused by a disease are revealed with Raman spectroscopy [6].

Neurodegenerative diseases are not localised to the inaccessible brain – protein aggregates are formed in various tissues in the body, but affect the physiological functioning of neurons first. Raman spectroscopy has been applied to various neurodegenerative diseases [7]. Parkinson's was diagnosed with an accuracy of 71% by investigating circulating extracellular vesicles filtered from the blood [8]. Alzheimer's has received the greatest focus from researchers. Raman spectroscopy of blood serum was able to differentiate patients with more than 95% sensitivity and specificity [9]. Raman spectroscopy of Lewy Bodies in blood [10] achieved 84% sensitivity and 86% specificity in predicting *early stage* Alzheimer's. In our proof-of-concept experiments, we applied Raman spectroscopy to a minipig model of Huntington's disease [11], and found an impressive diagnostic accuracy of 96% (area under curve) for both brain and skin tissue – see Fig. 1 – for a PLS-DA discriminator.

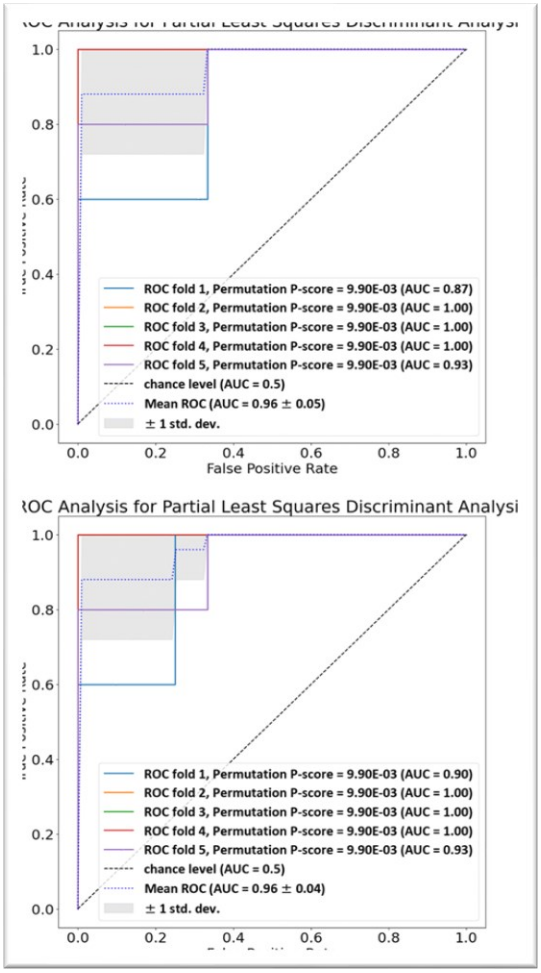

Fig. 1. Receiver operating characteristic curves showing performance of a classification model at all classification thresholds, for Huntington's disease of brain (top) and skin (bottom) using PLS-DA. [11]

Research Challenge

In collaboration with the project partners Tom Russ (clinician, Network champion for the NHS Research Scotland Neuroprogressive and Dementia Network, head of Alzheimer Research Scotland), we will approach newly diagnosed patients - first with Alzheimer's; then Parkinson's, Huntington's, motor neurone disease, and fronto-temporal dementia. Patients and volunteers will provide both urine and blood samples, and the student will acquire and process Raman spectra.

Data & Methodology

Spectral pre-processing techniques will be improved and optimised, then machine learning (ML) techniques applied to classify samples as healthy or diseased. Beyond a test for a single disease, we will combine all diseases into a single test to determine overall accuracy, and determine how accurately diseases can be distinguished. The next step is extraction of signature Raman peaks. The curated spectrum will be used to both assess the presence of molecular biomarkers and for downstream analysis through an ensemble of ML classifiers and clustering approaches. Classifiers will be trained on ground truth data validated through alternate tests, and the clustering approach will be

used to uncover latent characteristics and groups of diseases to improve the identification of a single disease among many possible.

We also plan to monitor patients with Alzheimer's over time, from diagnosis over the course of the disease during the project. This will allow our partner clinician to monitor the patient better, and determine whether the patient response to treatments show signs of slowing disease progression. We will use a generative approach, akin to latent growth model, to track the abundance of biomarkers within the Raman spectra within an individual patient, and we will use a similar approach to model a group of patients with the assumption that they will share similar characteristics of disease progression. Models will be extended to allow change point detection to explore if a treatment has the effect of changing the course of the disease.

Responsible AI/Ethical Considerations

We will conduct interaction with patients groups via Partners In Research – a Public / Patient Involvement (PPI) group involving carers. Data handling will be planned with guidance from Carol Porteous (University of Edinburgh PPI Lead).

Expected Outcome & Impact

We plan to produce an accurate, multi-disease test for neurodegenerative diseases, applicable to clinical diagnose as well as population screening. Subsequently, we will apply for funding of larger patient studies (clinical trials) as a pathway to implementation in the NHS.

References

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