Understanding Aging and Neurodegeneration using a Contrastive Learning Approach on NMR Data

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Background

Understanding the molecular mechanisms underlying aging with regards to neurodegeneration is a fundamental goal in biomedical research, with implications for improving healthspan and longevity. High-throughput techniques such as Nuclear Magnetic Resonance (NMR) spectroscopy enable comprehensive profiling of serum metabolites, allowing researchers to detect subtle alterations associated with aging. Using principal component analysis (PCA), however, tends to factor is noise from metabolites that is not of interest. Using contrastive PCA, the background noise can be subtracted to focus on biological relevance [1].

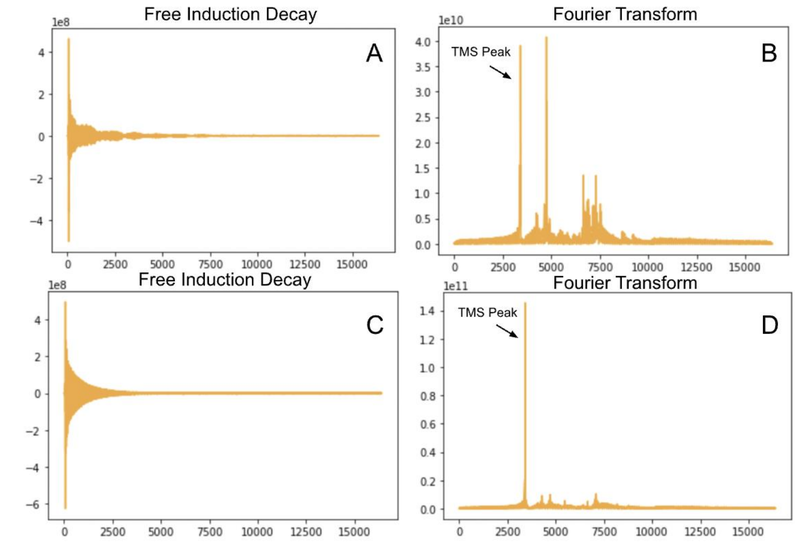

Figure 1: NMR spectra comparing serum samples of mice at different ages and human serum. Free Induction Decay of serum from 6-month-old mice (A). 6-month-old mice NMR data after preprocessing (FFT, discarding imaginaries and taking absolute) (B). Free Induction Decay of background human serum (C). Background NMR data after preprocessing (D).

Methods

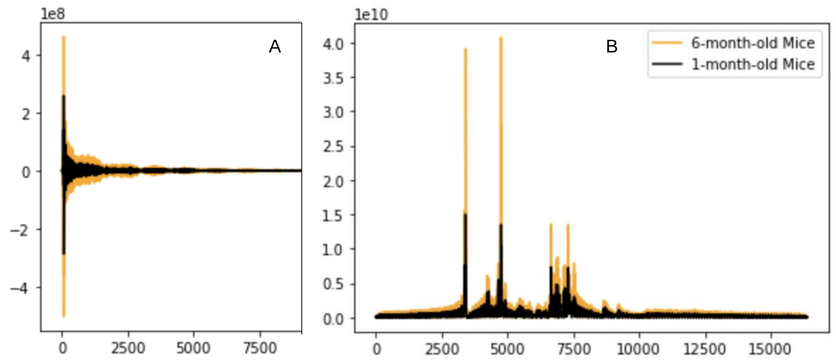

Figure 2: Free Induction Decay NMR Spectra of 1-month-old mice overlayed on 6-month-old mice, showing differences in metabolite peaks (A). Processed NMR data of 1-month-old mice overlayed on 6-month-old mice (B).

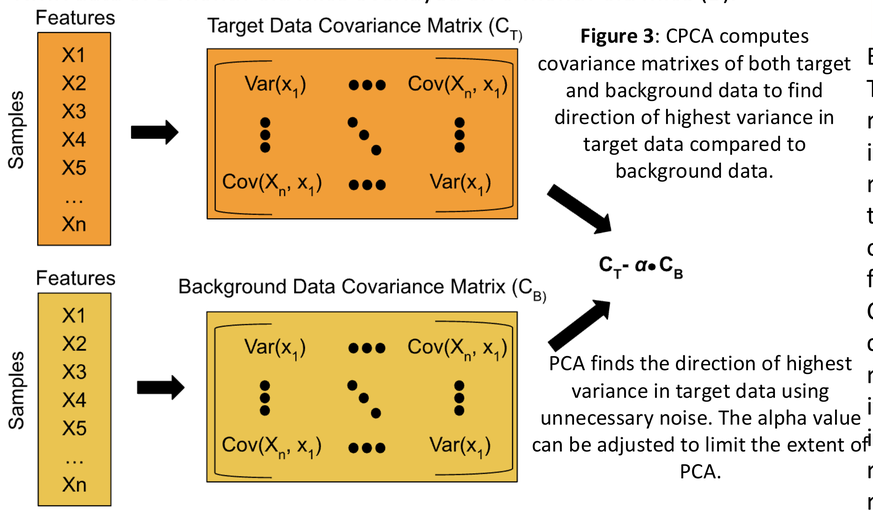

Figure 3: CPCA computes covariance matrixes of both target and background data to find direction of highest variance in target data compared to background data.

$C_T - \alpha \bullet C_B$

PCA finds the direction of highest variance in target data using unnecessary noise. The alpha value can be adjusted to limit the extent of PCA.

Following preprocessing steps, the 1-month-old and 6-month-old mice NMR data were fed into principal component analysis to reduce the dimensionality. An added background dataset where metabolite noise was leached through dialysis of human serum, was fed into contrastive PCA to identify a direction of variance in solely biologically relevant data [2].

Results

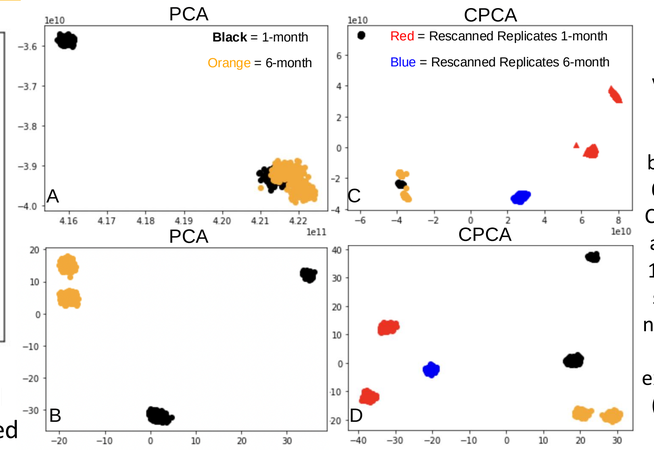

Figure 4: Principal components 1 and 2 visualized as clusters. PCA shows lack of distinct separation between 1-month and 6-month samples (A). Contrastive PCA shows a separation between 1-month and 6-month samples, background noise was removed (B). PCA with rescanned experimental replicates (C). CPCA with rescan replicates (D).

Analysis

Each cluster contains technical replicates collected from a single scan. Thermal noise between samples causes the distribution of these technical replicates. There were also biological replicates, which correspond to the individual clusters, which result from different scans. Lastly, experimental replicates were considered which were taken at a vastly different timepoint, and the serum could have undergone aging processes such as oxidation. As seen from PCA, the old mice could not be separated clearly from the young mice. After accounting for the background noise using CPCA, the young and old samples can be clearly differentiated and classified in their appropriate categories. When including the experimental replicates, CPCA performed better at grouping the old and young mice, but it focused on distinguishing between the experimental timepoints [3]. The initial samples were scanned following defrosting. The same samples were rescanned after a week (experimental replicates). The differences in these replicates can be attributed to oxidation. For next steps, more oxidized serum samples can be collected, and solid tissue samples can be analyzed.

References

1. Abid, A., Zhang, M.J., Bagaria, V.K. *et al.* Exploring patterns enriched in a dataset with contrastive principal component analysis. *Nat Commun* **9**, 2134 (2018). https://doi.org/10.1038/s41467-018-04608-8
2. Aidas Aglinskas et al., Contrastive machine learning reveals the structure of neuroanatomical variation within autism.Science376,1070-1074(2022). DOI:10.1126/science.abm246
3. Abid, Abubakar, et al. "Contrastive Principal Component Analysis." arXiv.org, 20 Sept. 2017, arxiv.org/abs/1709.06716.

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