Predicting Disease Progression Trajectories in Individuals with Amyotrophic Lateral Sclerosis using Multimodal Digital Biomarkers

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Methodological Question and Introduction

- **Disease progression in Amyotrophic Lateral Sclerosis** (ALS) is **heterogeneous** due to the varying presentation of clinical symptoms.This heterogeneity complicates the **quantification of longitudinal disease severity** and the assessment of **therapeutic efficacy**.
- Many models **assume** a **linear decline in ALSFRS-R**, the clinical gold-standard to measure disease state, but evidence suggests **non-linear progression** over time.
- This study explores a **non-linear model** to predict **individual disease trajectories** in people with ALS (pALS) using **dense or sparse multimodal data**.

Research Question 1 (RQ1) *Disease trajectory prediction:* Given a set of non-uniformly sampled digital biomarkers and the clinical-standard ALSFRS-R score over an 8-week time period, can individual disease progression trajectories be predicted for the 8-week period that immediately follows?

Research Question 2 (RQ2) *Sparse trajectory prediction:* How well can we predict disease time-course (as in RQ1) for a desired future time-point (at 16 weeks) when multimodal digital biomarkers and the ALSFRS-R score are sparsely sampled (only two time points per participant - one at baseline and one at 8 weeks)?

Data and Methods

	Number of participants	Number of sessions	Mean age ± SD (years)
Bulbar onset	36 (18 female)	581	61.6 ± 11.9
Non-bulbar onset	107 (52 female)	2833	59.9 ± 9.6

Table 1: Demographics

- Data collected using a **cloud-based multimodal dialogue platform** (Illustration in Figure 1)
- **Tina, a virtual guide,** walked participants through structured speaking exercises and **objective metrics** were extracted.
- **Tasks**:
  - Read speech (**sentence intelligibility test (SIT);**
    Reading Passage (**RP**; Bamboo passage 99 words)
  - **Oral diadochokinesis (DDK)**
  - **Picture description task (PD)**
- We used ***leaspy***, a software package for the statistical analysis of longitudinal medical data in the form of repeated observations at various time-points.
- We trained Bayesian logistic mixed effects models to predict individual trajectories of 17 features - that can distinguish pALS with bulbar onset from those with non-bulbar onset (Neumann & Kothare *et al.*, 2024), the total ALSFRS-R score, ALSFRS-R bulbar subscore and the ALSFRS-R speech score.
- For RQ1, we predicted weeks 8 to 16 using the first 8 weeks of data. For RQ2, we predicted week 16 based on baseline (week 0) and week 8. Model performance, tested via leave-one-out cross-validation, was evaluated using normalized mean absolute error (nMAE) to account for feature range differences.

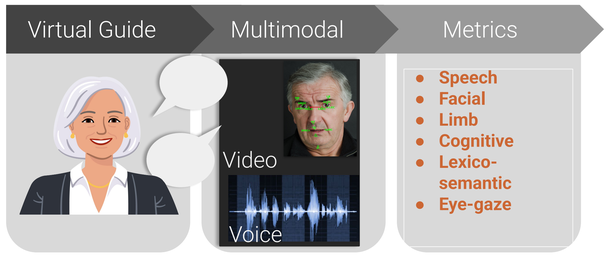

Figure 1. Schematic of the Modality dialogue platform

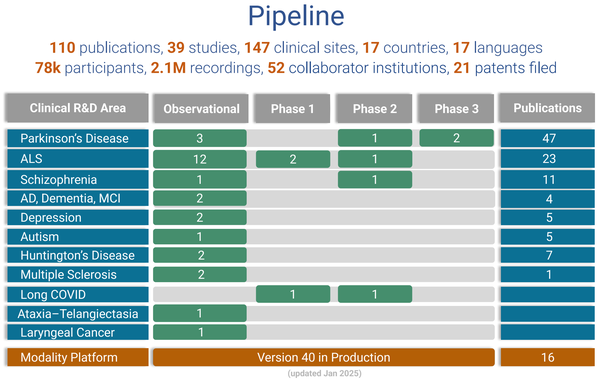

Figure 2. Schematic of the current Modality pipeline

Results and Discussion

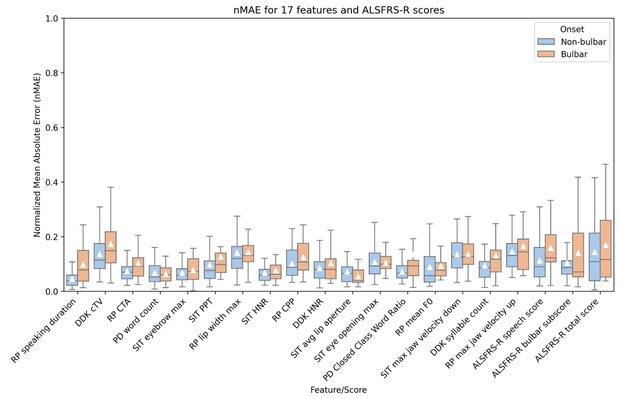

Figure 3 (RQ1 results) Normalized mean absolute error values (nMAE) for 17 features and ALSFRS-R scores over an 8-week period. White triangle = mean value across pALS, horizontal line = median value across pALS.

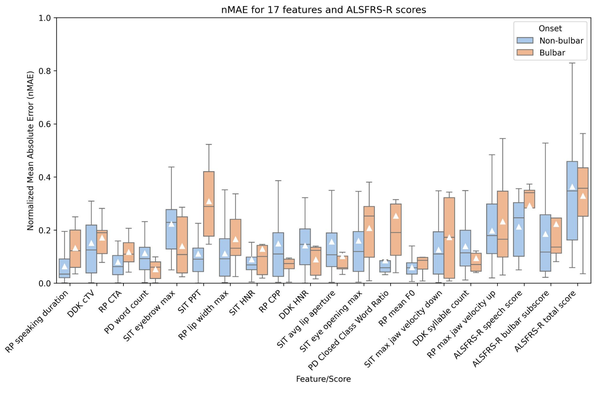

Figure 4 (RQ2 results) Normalized mean absolute error values (nMAE) for 17 features and ALSFRS-R scores at week 16 with sparse sampling at week 0 and week 8. White triangle = mean value across pALS, horizontal line = median value across pALS.

- **RQ1:** nMAE was < 0.2 for all features and scores The best performance was for speaking duration of RP (nMAE = 0.06). The worst performance was for maximum upward jaw velocity for the reading passage and the ALSFRS-R total score (nMAE = 0.15).
- **RQ2:** Model performance is good for digital biomarkers but worse in predicting the ALSFRS-R speech score and bulbar subscores as compared to disease trajectory prediction with denser data. The best performance was for speaking duration and mean F0 of RP (nMAE = 0.08). The worst performance was for the ALSFRS-R total score (nMAE = 0.35).
- In most cases in RQ1, the nMAE was lower for non-bulbar pALS than bulbar pALS.
- Such non-linear models have the potential to help with stratification of pALS into fast and slow progressors and thus inform treatment approaches. Patient stratification is also a key factor in designing clinical trials to test the efficacy of drugs in slowing progression.

Conclusions

The results suggest that that non-linear models using multimodal digital biomarkers offer more promise and precision than the current clinical standard for predicting individual disease progression trajectories in ALS.

References

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