AD i.d.e.a. – Alzheimer's Disease integrated dynamic electronic assessment of Cognition

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Background

Assessing a persons cognitive ability is a challenging and time consuming process, yet essential for the diagnosis and monitoring of patients with Alzheimer's disease (AD). Existing cognitive tests are either quick, e.g., mini-mental state examination (MMSE) [1], or precise, e.g., ADAS-cog [2], but fail to be both. The objective of this project was to develop a procedure that achieves both, by combining pharmacometric methods with the capabilities of a modern Web application, and creating an integrated dynamic electronic assessment of cognition in Alzheimer's disease.

Methods

IRT Model: A NLME model using the item response theory approach (IRT) previously developed for the ADAS-cog assessment from trial database data (ADNI & CAMD) was used[3]. The model describes response probabilities (binary, binomial and ordered categorical type) for assessment items as a function of subject-specific cognitive disability D_i and item-specific parameters θ_j:

$$P(Y_{ij} = k) = f_j(D_i, \theta_j) \quad (1)$$

ADAS-cog model was extended to the MMSE assessment through additional response functions (all failed/succeeded type) with same hidden variable (test parameters determined using ADNI data):

$$P(Y_{ij}^{MMSE} = 1) = \frac{e^{a_j(D_i - b_j)}}{1 + e^{a_j(D_i - b_j)}} \quad (2)$$

Adaptive Testing Algorithm: Cognition assessment is performed adaptively using the IRT model and the following 3 step iterations:

1. Previous patient responses and the population prior for disability are used to determine an estimate for the patient's disability:

$$\widehat{D_i} = \arg\max \mathcal{L}(D_i|Y_i) \quad (3)$$

$$\mathcal{L}(D_i|Y_i) = \log p(Y_i|D_i) + \log p\left(D_i\middle|\omega_{Di}^2\right) \quad (4)$$

   as well as uncertainty information:

$$Var\left(\widehat{D_i}\right) = \left(\frac{d^2\mathcal{L}(D_i|Y_i)}{dD_i^2}\right)^{-1} \quad (5)$$

2. Expected Fisher information is calculated for all tests in the database

$$E(I_j) = \int_{-\infty}^{\infty} p\left(x\middle|\widehat{D_i}, Var\left(\widehat{D_i}\right)\right) I_j(x)\, dx \quad (6)$$

3. Test with highest expected information is selected, presented to the patient, whose response is recorded to obtain refined estimates in the next iteration

Web Application: Adaptive test selection and storing of patient responses are handled on the server-side through a Ruby on Rails based web application with connection to a SQLite database. On the client-side, the user interface will be implemented using HTML5 and JavaScript in a responsive design paradigm to optimize usability for wide a range of devices (from smartphone to desktop).

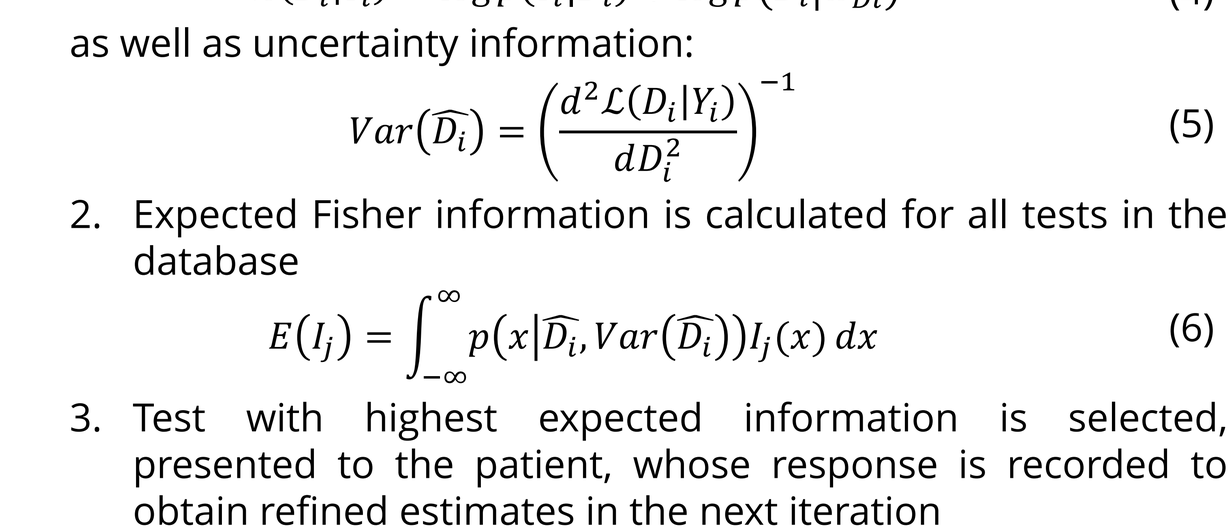

Fig.1: Application architecture and web technologies utilized

Results

Algorithm validation:

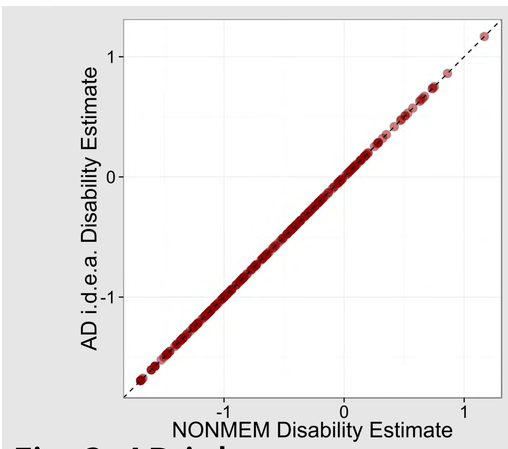

Fig. 2: AD i.d.e.a. versus NONMEM disability estimates

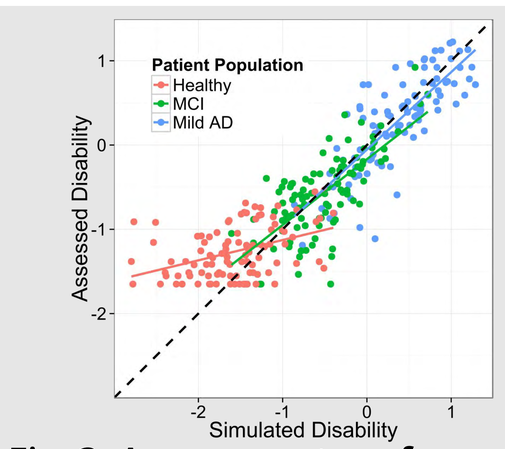

Fig. 3: Assessment performance for 3 patient populations

Algorithm operation:

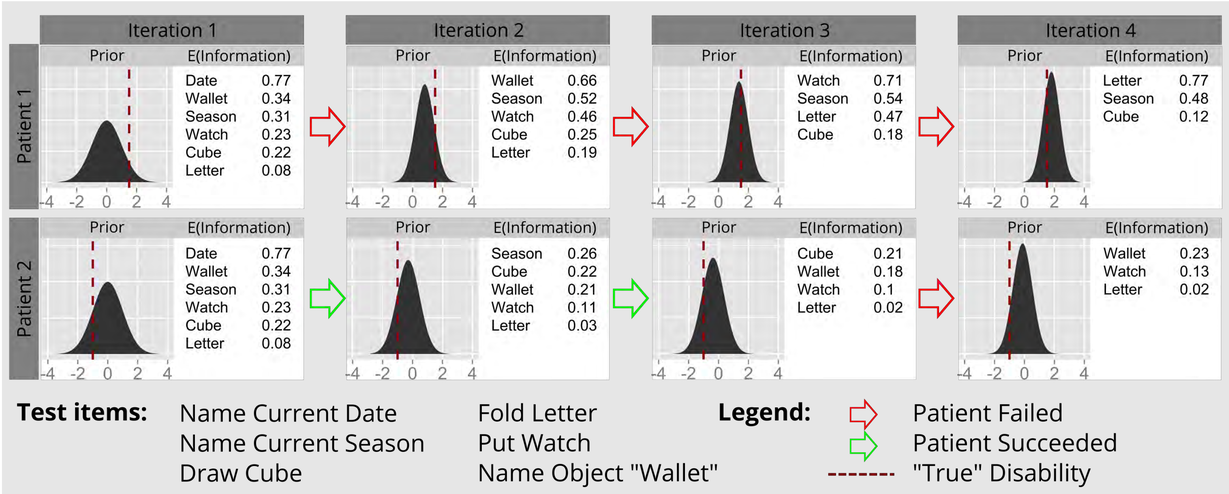

Fig. 4: First 4 iterations of adaptive testing algorithm for 2 exemplary patients (reduced test item database)

Performance comparison:

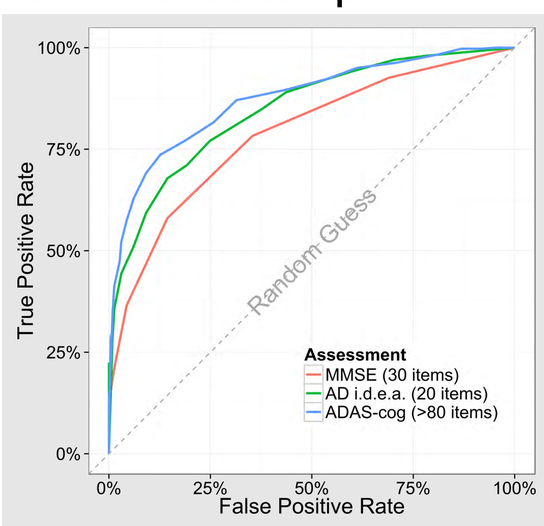

Fig.5: ROC curves comparing assessment suitability as binary "healthy-cognitively impaired" classifier

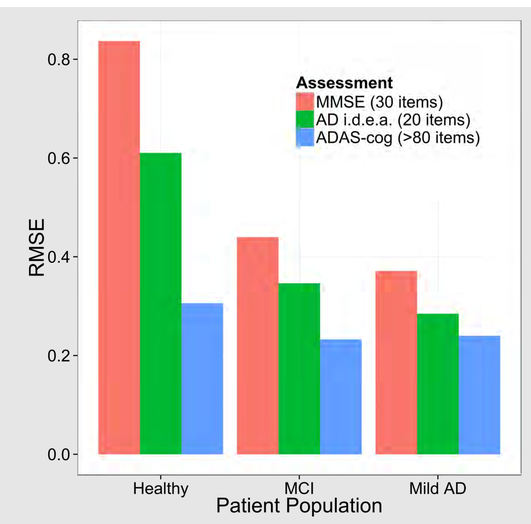

Fig.6: Root mean squared error (RMSE) for estimating disability in different populations using different assessments

Conclusions

AD i.d.e.a. web application:

- ❖ Reduced assessment time or increased precision (depending on stopping rule)
- ❖ More frequent evaluations by varying tests between visits
- ❖ Operation as diagnostic and monitoring tool
- ❖ Translation of pharmacometric method into clinical tool

References:

1. Folstein et al. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189-98..
2. Rosen et al. A new rating scale for Alzheimer's disease. Am J Psychiatry. 1984 Nov;141(11):135664.
3. Ueckert et al. Application of Item Response Theory to ADAS-cog Scores Modelling in Alzheimer's Disease. PAGE 21 (2012).

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