



FORECAST ALZHEIMER'S DISEASE PROGRESSION TO BETTER SELECT PATIENTS FOR CLINICAL TRIALS

Etienne Maheux, Juliette Ortholand, Colin Birkenbihl, Elina Thibeau-Sutre, Meemansa Sood, Damiano Archetti, Vincent Bouteloup, Igor Koval, Stanley Durrleman







Introduction

Disease course mapping with *Leaspy*

Clinical trial simulation

Conclusion







Introduction







Alzheimer's Disease clinical trials keep failing for several reasons, among which :

« The lesson to be derived from these studies is that sponsors should seek ways of minimizing variability in global trials to insure greater data homogeneity » Cummings, J. (2017). <u>Lessons</u> <u>Learned from Alzheimer Disease: Clinical Trials with Negative Outcomes.</u> <u>Clinical and Translational Science</u>

Our approach – using prediction to target the right patients at trial screening –

is a way to reduce the needed sample size or conversely to improve the proven effect size.







Disease course mapping with Leaspy

Application to forecasting at individual level







A Bayesian mixed-effects model to learn trajectories of changes from repeated manifold-valued observations



Fig 1 : Individual parameters of our disease course maps







A Bayesian mixed-effects model to learn trajectories of changes from repeated manifold-valued observations



Fig 1 : Individual parameters of our disease course maps







We use past individual data to position a subject on the Disease Course Map, and we then predict how the subject's biomarkers will change in the next few years. [4]



Fig 2 : From average model to individuals predictions and evaluation







Clinical trial simulation







In this part we simulate EMERGE/ENGAGE Phase 3 clinical trial using retrospective AD observational data

« Must meet all of the following clinical criteria for MCI due to AD or mild AD and must have:

- A Clinical Dementia Rating (CDR)-Global Score of 0.5.
- *Objective evidence of cognitive impairment at screening*
- An MMSE score between 24 and 30 (inclusive)
- Must have a positive amyloid Positron Emission Tomography (PET) scan »

Source: <u>ClinicalTrials.gov</u>

Our aim is to add a selection criteria based on individual forecast of clinical trial outcome







We first train Disease Course Maps from individual snapshots of AD progression



Fig 3 : Average progression model learnt on discovery cohort







We then personalize the trained model, to predict outcome

- from individual's screening biomarkers
- > at the *end* of the clinical trial



Fig 5 : Selection of prediction tasks for a run

Fig 6 : Generation of forecasts









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We use 5 datasets to get as much patients as possible to simulate the trial

	Subjects	Visits	Follow-up duration (y)	Delay between visits (m)	Age at baseline (y)	Female
ADNI	1599	6.1 ± 2.8	4.7 ± 3.0	11.1 ± 6.3	73.4 ± 7.1	744 (46.5 %)
AIBL	460	3.7 ± 0.7	4.1 ± 1.0	18.2 ± 2.0	71.5 ± 7.1	247 (53.7%)
J-ADNI	469	5.1 ± 0.8	2.7 ± 0.5	7.8 ± 2.8	71.8 ± 6.7	246 (52.5%)
MEMENTO	1995	6.8 ± 1.8	3.7 ± 0.7	7.7 ± 3.4	70.6 ± 8.6	1216 (61.0%)
PHARMACOG	111	5.1 ± 0.6	2.0 ± 0.3	6.0 ± 0.6	69.8 ± 7.4	63 (56.8%)
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Fig 7 : Available datasets for trial simulation

	Forecasts	Subects	Forecasts per subject	Trial duration (y)	Age at screening	Female
Pooled	3238	906	3.6 ± 2.5	1.4 ± 0.4	73.0 ± 6.9	1490 (46%)
ADNI	1721	572	3.0 ± 2.1	1.4 ± 0.3	74.0 ± 6.8	706 (41%)
AIBL	6	5	1.2 ± 0.4	1.5 ± 0.0	77.6 ± 4.0	3 (50%)
J-ADNI	378	74	5.1 ± 2.7	1.4 ± 0.4	72.5 ± 5.7	191 (51%)
MEMENTO	679	172	3.9 ± 2.9	1.4 ± 0.3	72.4 ± 7.2	339 (50%)
PHARMACOG	454	83	5.5 ± 2.7	1.3 ± 0.4	70.4 ± 7.0	251 (55%)

Fig 8 : Datasets of forecasts for the clinical trial





Clinical trial simulation



We identify fast progressors thanks to our forecasts 80%



Fig 9 : Enrichment results for EMERGE clinical trial



We simulate the whole trial with hypothetical treatment effect to get an idea of how our selections improve global effect size.





Selections enable to reduce the number of patients needed to observe a given treatment effect.



Fig 12 : Results for EMERGE clinical trial







Conclusion







Take home messages:

- We developed a Disease Course Mapping that can be used to forecast at individual level
- Our predictions enable to select more homogeneous and relevant sub-groups of patients
- Stratifying patients with predictions in AD trials can help improving effect size

Future directions:

- Working on real clinical trial data
- Application to other neurological diseases







Some references

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Thank you for your attention



gitlab.com/icm-institute/aramislab/leaspy



www.aramislab.fr



