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# A multivariate bayesian mixed-effect model (Leaspy) to analyze the trajectory of cognitive decline in CADASIL

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## Introduction

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), the most frequent cerebral small artery disease is caused by stereotyped mutations of the NOTCH3 gene. The multifaceted clinical presentation of this disorder can be assessed using various measures<sup>[1]</sup>. We used a bayesian mixed effect model(Leaspy) to model the multivariate disease progression and explore the spatiotemporal relationships between these measures. We were also able to identify different groups of individual evolution according to the time shift and acceleration rate by taking into account the gender, education level, smoking, hypertension and the mutation's position.

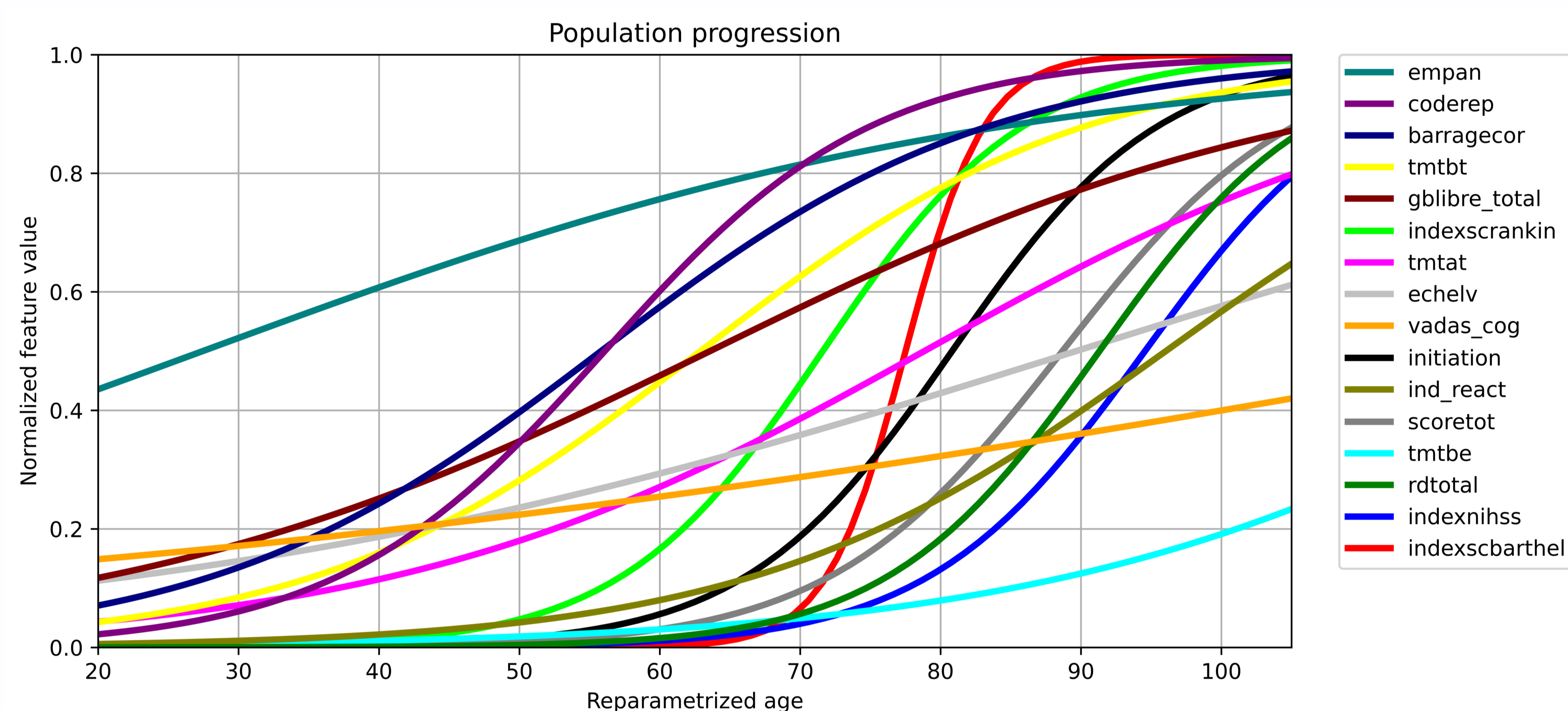
## Data & Method

We analysed data obtained from **395** patients recruited at the French National Referral Centre CERVCO across a median number of **4 visits** per individual (IQR:3-7) (total visits: **2007**). The follow-up duration varied from 6 months to 19 years with a median interval of **6.5 years** (IQR:3.5-11). They were 45% men, 72% with a high school diploma or less, 18% current smokers and 21% presenting hypertension with a median inclusion age of 53 years (IQR:45-61). They were 66% presenting the mutation in the EGFr domains considered as high risk 1-6,8,11 and 26<sup>[2]</sup>.

The outcomes analyzed were **16 clinical scores** measuring cognitive efficiency, cognitive speed and mental flexibility, memory performance, life quality, disability and neurological deficits.

We used a logistic multivariate **bayesian mixed-effect model**(Leaspy) to analyze the progression of these outcomes. As with every mixed effect model we obtained the fixed effects (population parameters representing the shape and position of logistic curves) and the random effects (individual parameters that represent the time shift ( $\tau$ ), acceleration rate ( $\xi$ ) and inter-marker spacing). The bayesian framework allowed us to minimize the errors between the estimated curves and the individual timepoints by performing iteratively joint estimations of these parameters. Leaspy also offered us the advantage to model the evolution without knowing the exact time of the disease onset for each individual.

## Results

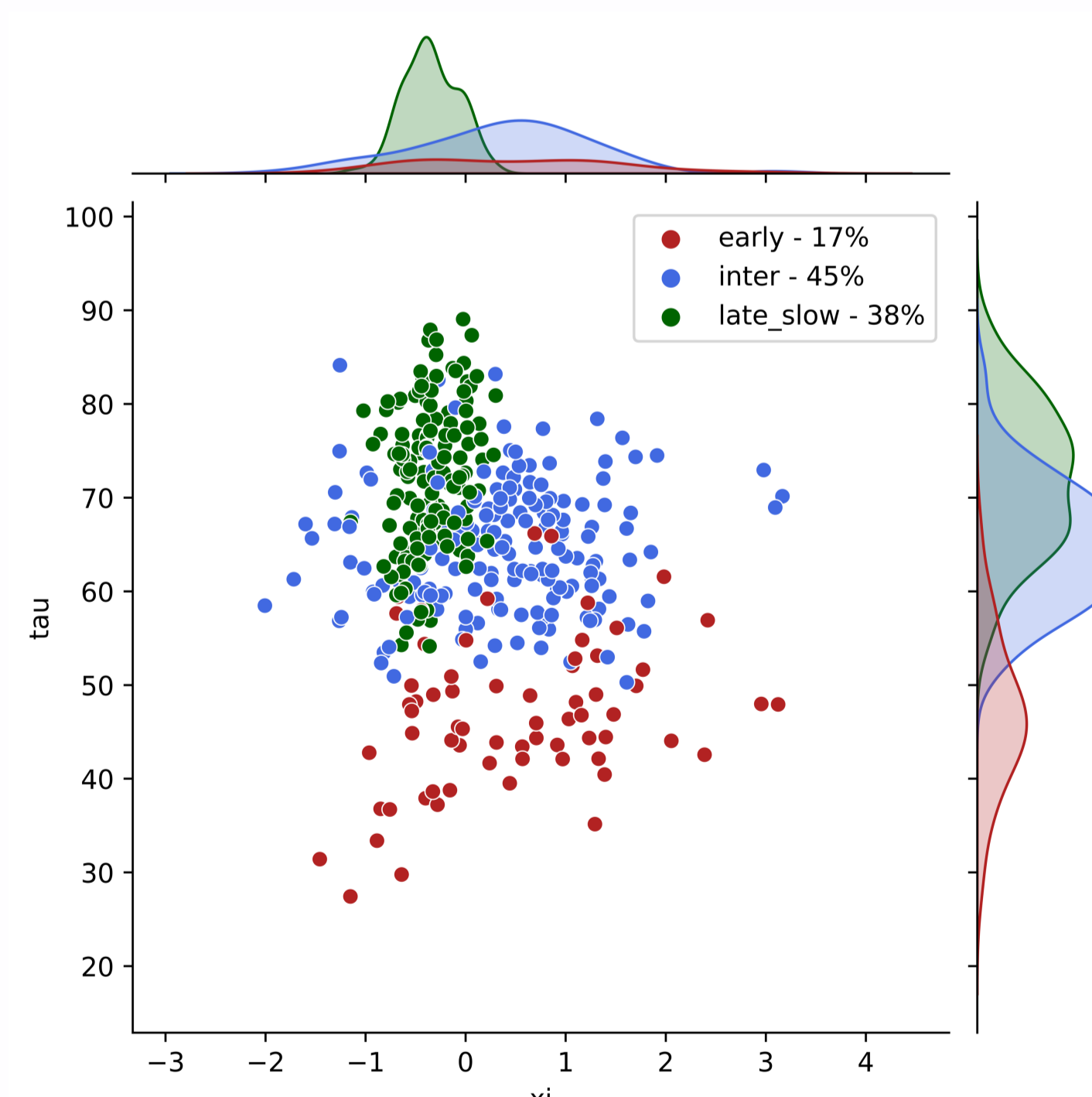


According to the **population parameters** describing the starting acceleration point of the logistic curves we were able to distinguish 3 groups of evolution :

**Early age** : VADAS-Cog Backward digit span (empan), VADAS-Cog Symbol digit test (coderep), VADAS-Cog Digit cancellation task (barragecor), Trail making test B time (tmtbt) , Grober & Buschke total free recall (gbllibre\_total)

**Mid age** : Rankin index (indexscrankin), Trail making test A time (tmtat), VAS Quality of life (echelv), VADAS-Cog Total score (vadas\_cog)

**Late age** : Mattis DRS Initiation (initiation), Grober & Buschke index of sensitivity to cueing (ind\_react), Mattis DRS Total Score (scoretot), Trail making test B errors (tmtbe), Grober & Buschke delayed total recall (rdtotal), NIHSS index (indexnihss), Barthel index (indexscbarthel)



We implemented a Gaussian Mixture Model classification for the **individual Leaspy parameters** describing the temporal variability( $\tau$  and  $\xi$ ) and the 5 covariables that showed significant interactions with these parameters in the non-parametric tests (gender, education level, smoking, hypertension and the position of the mutation). As a result, we got a group of patients that show early evolution ( $\bar{\tau}_i=47$ ,  $\bar{\xi}_i=0.5$ ), a group of intermediate ( $\bar{\tau}_i=65$ ,  $\bar{\xi}_i=0.3$ ), and a group of late and slow evolution ( $\bar{\tau}_i=72$ ,  $\bar{\xi}_i=-0.3$ ).

## Conclusion

- Cognitive alterations develop heterogeneously during the progression of CADASIL and vary widely according to the stage of the disease.
- The disease progresses more aggressively for patients that are male, less educated, smokers, presenting hypertension and having the mutation in the EGFr domains 1-6,8,11 and 26.

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