Modeling inter-related longitudinal processes in cerebral aging

Cécile Proust-Lima
based on PhD Thesis of Bachirou Taddé

INSERM U1219, Bordeaux Population Health Research Center, Bordeaux, France
Univ. Bordeaux, ISPED, Bordeaux, France
cecile.proust-lima@inserm.fr

Automn Meeting of BMS-ANed - Biostatistics Kaleidoscope
November 20, 2020

Context

- Alzheimer's disease (AD)
  - most frequent type of dementia in the elderly
  - occurs mostly after 65 years old for the sporadic (non familial) form

- Very long progression before clinical diagnosis (several decades)

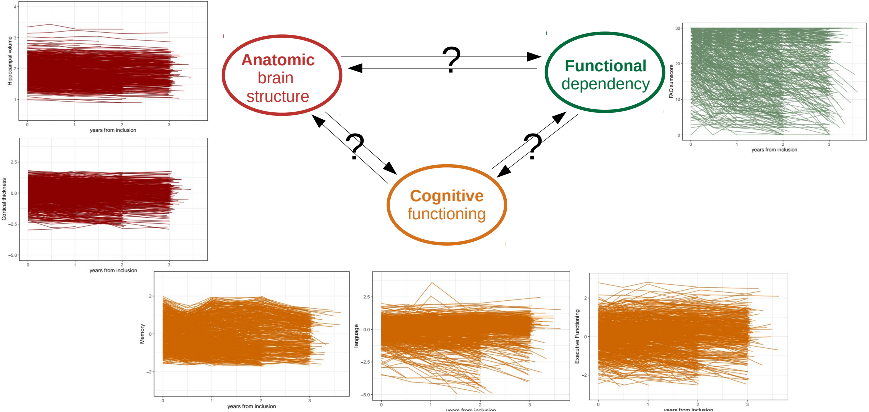
- Multiple anatomo-clinical impairments :
  - accumulation of biomarkers in the brain (beta-amyloid, tau-protein)
  - atrophy of some brain regions (e.g., hippocampus)

  - cognitive decline (e.g., langage, memory)
  - impaired functional dependency (mobility, daily living activities)

  - depressive symptomatology, anxiety, ...

Challenge

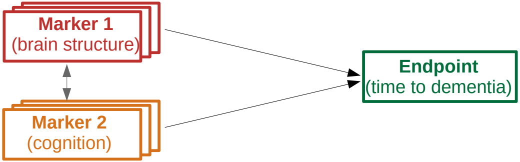
- How to understand the temporal influences between the multiple dynamic domains involved in AD development ?



i.e., How to quantify temporal associations between dynamic processes ?

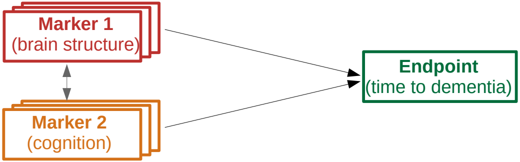
What can we do ?

- If the endpoint is a time-to-event :
  - We can run joint models for longitudinal and event history data
  - We assess the effect of repeated biomarkers $Y_1(t)$ and $Y_2(t)$ on the instantaneous risk of event $\lambda(t)$

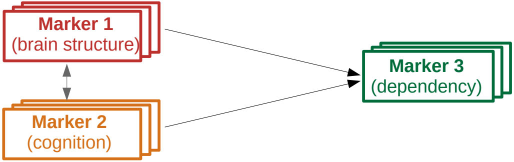


What can we do ?

- If the endpoint is a time-to-event :
  - We can run joint models for longitudinal and event history data
  - We assess the effect of repeated biomarkers $Y_1(t)$ and $Y_2(t)$ on the instantaneous risk of event $\lambda(t)$



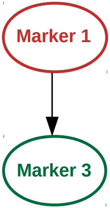
- But what if the endpoint is a marker measured repeatedly over time ?
  - We want to assess the effects (or temporal associations) of repeated biomarkers $Y_1(t)$ and $Y_2(t)$ on the dynamics of $Y_3(t)$



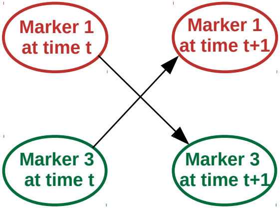
Temporal relationships in the literature

- Using Directed Acyclic Graphs (DAG)
  - Framework :

Cross-sectional



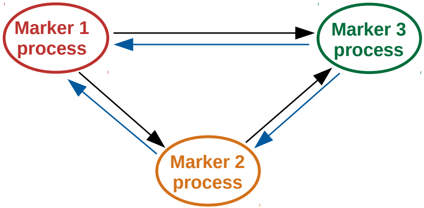
Repeated visits



  - Direct arrow :
    Effect of the level of one dimension on the subsequent level of another one
  - Models : Structural Equation Models, Dynamic Bayesian Networks
  - Limits : based on the discrete visit process (Aalen et al., 2016)
    + associations between levels only

Temporal relationships in the literature (cont'd)

- Using Local Dependence Graphs (LDG) (Didelez, 2008)
  - Framework :
    Longitudinal (continuous time with latent processes)



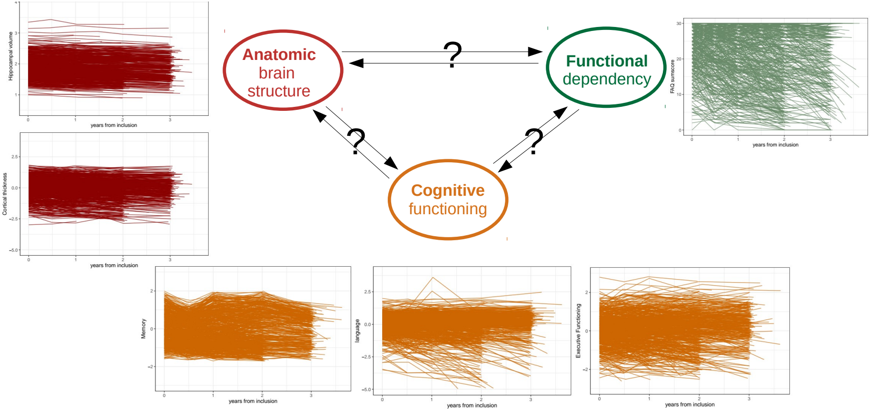
  - Direct arrow : Effect of the level of one dimension on the subsequent change of another - e.g. effect of $\Lambda_1(t)$ on $\frac{d\Lambda_3(t)}{dt}$
  - Models : mechanistic models, differential equations
  - Advantages : separation from the visit process
    + focus on the dynamics (Voelkle et al., 2018)
  - Limits : Numerically very complex

Our contribution

- Define a dynamic model to quantify the temporal links between dimensions measured repeatedly over time
- Apply the methodology to the processes involved in Alzheimer's disease

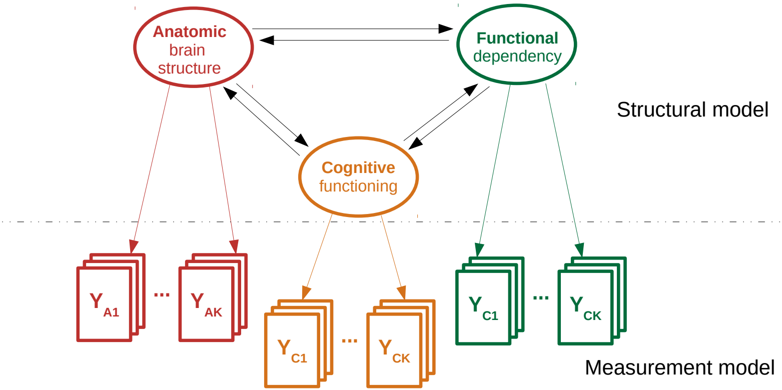
Our contribution

- Define a dynamic model to quantify the temporal links between dimensions measured repeatedly over time
- Apply the methodology to the processes involved in Alzheimer's disease



Our contribution

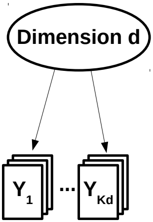
- Define a dynamic model to quantify the temporal links between dimensions measured repeatedly over time
- Apply the methodology to the processes involved in Alzheimer's disease



Measurement models

Each latent dimension d : $(\Lambda_{di}(t))_t$

is repeatedly measured by K_d markers
(possibly non Gaussian) :



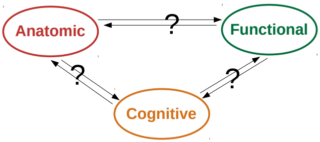
$$H_{dk}(\ Y^d_{kij}\ ; \eta_{dk}\ ) \ = \ \Lambda_{di}(t_{dkij}) + \epsilon^d_{kij} \qquad \text{for } k = 1, ..., K_d$$

with $\epsilon^d_{kij} \sim \mathcal{N}(0, \sigma^{d^2}_k)$ and H_{dk} flexible parameterized link function
(e.g., linear combination of quadratic I splines)

Structural model for the underlying dimensions

Initial level of each process d $(d = A, F, C)$

$$\Lambda_{di}(0) = X_i^0 \beta_d + u_{di}$$



Change of the processes over finely discretized time (step δ)

$$\frac{\Lambda_{Fi}(t+\delta)-\Lambda_{Fi}(t)}{\delta} = X_{Fi}(t)\gamma_F + Z_{Fi}(t)v_{Fi} + \alpha_{FF}\Lambda_{Fi}(t) + \alpha_{CF}\Lambda_{Ci}(t) + \alpha_{AF}\Lambda_{Ai}(t)$$

$$\frac{\Lambda_{Ci}(t+\delta)-\Lambda_{Ci}(t)}{\delta} = X_{Ci}(t)\gamma_C + Z_{Ci}(t)v_{Ci} + \alpha_{FC}\Lambda_{Fi}(t) + \alpha_{CC}\Lambda_{Ci}(t) + \alpha_{AC}\Lambda_{Ai}(t)$$

$$\frac{\Lambda_{Ai}(t+\delta)-\Lambda_{Ai}(t)}{\delta} = X_{Ai}(t)\gamma_A + Z_{Ai}(t)v_{Ai} + \alpha_{FA}\Lambda_{Fi}(t) + \alpha_{CA}\Lambda_{Ci}(t) + \alpha_{AA}\Lambda_{Ai}(t)$$

- identifiability constraint : $\Lambda_{di0}|_{X_{i0}} \sim \mathcal{N}(0,1)$
- subject i, time t, discretization step δ
- $(u_{1i}, \ldots u_{Di}, v_{1i}, \ldots, v_{Di})^\top \sim \mathcal{N}(0, B)$

Maximum Likelihood Estimation for parameters θ

- Gaussian framework for the estimation :
  - $\Lambda_i = \{\Lambda_{dit} \; ; \; d = A, C, F \; , \; t \in \tau_i\} \sim \mathcal{N}\left(\mu_i ; V_{\Lambda_i}\right)$
    (with μ_i and V_{Λ_i} quite complex though)
  - Jacobian formula for the link functions

  = Exact likelihood formula

- Maximization with the parallelized Marquardt algorithm `marqLevAlg` (Philipps et al., 2020)

- Validated by simulations
  - with transition matrix constant or time dependent

Assessment of the impact of time discretization

- Simulation study :
  - 3 dimensions, linear trajectory over time
  - generation model in continuous time (δ=0.001)
  - estimation with discretization steps δ=1/3, δ=1/2, δ=1

- Type I error over 1000 replicates (in %)

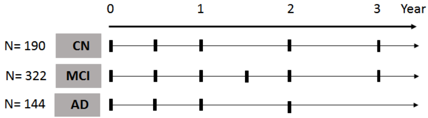
	$\delta = 1/3$	$\delta = 1/2$	$\delta = 1$
α_{12}	5.4	4.9	6.5
α_{13}	5.3	5.3	8.6
α_{21}	5.6	6.0	7.5
α_{23}	4.7	6.0	4.1
α_{31}	5.4	5.2	7.1
α_{32}	4.5	4.8	4.8

expected in [3.6 ;6.4]

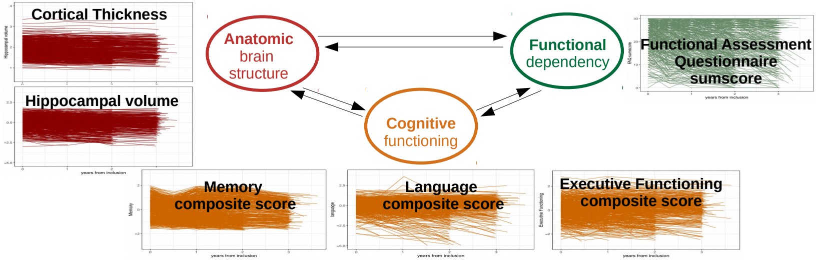
$\rightarrow$ Temporal influences not altered by the discretization when the step is reasonable

Data from ADNI-1 (Alzheimer's Disease Neuroimaging Initiative data)

- Prospective study that enrolled individuals at different aging stages :
  - Normal aging
  - Mild Cognitive Impairment
  - Diagnosed with Alzheimer's disease



- Three dimensions to explore and **contrast by stage** :

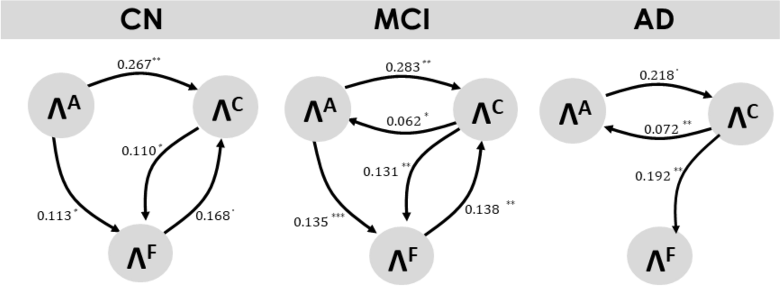


  - linear change over time for the dimensions
  - adjusted for age/sex/education/apoe4/**stage**

Estimates of the temporal influences

			Parameter	Estimate	SE	p-value
Influence on cerebral anatomy :						
	Effect of cognitive ability	Intercept	α^0_{AC}	0.014	0.015	0.377
		MCI	α^1_{AC}	0.048	0.018	0.008
		dAD	α^2_{AC}	0.058	0.027	0.030
	Effect of functional autonomy	Intercept	α^0_{AF}	0.015	0.031	0.627
		MCI	α^1_{AF}	-0.023	0.032	0.478
		dAD	α^2_{AF}	-0.040	0.037	0.286
Influence on cognitive ability :						
	Effect of cerebral anatomy	Intercept	α^0_{CA}	0.267	0.078	< 0.001
		MCI	α^1_{CA}	0.016	0.060	0.792
		dAD	α^2_{CA}	-0.049	0.080	0.535
	Effect of functional autonomy	Intercept	α^0_{CF}	0.168	0.096	0.079
		MCI	α^1_{CF}	-0.030	0.097	0.760
		dAD	α^2_{CF}	-0.034	0.113	0.766
Influence on functional autonomy :						
	Effect of cerebral anatomy	Intercept	α^0_{FA}	0.114	0.045	0.012
		MCI	α^1_{FA}	0.022	0.053	0.681
		dAD	α^2_{FA}	-0.053	0.069	0.441
	Effect of cognitive ability	Intercept	α^0_{FC}	0.111	0.049	0.023
		MCI	α^1_{FC}	0.021	0.053	0.696
		dAD	α^2_{FC}	0.082	0.072	0.259

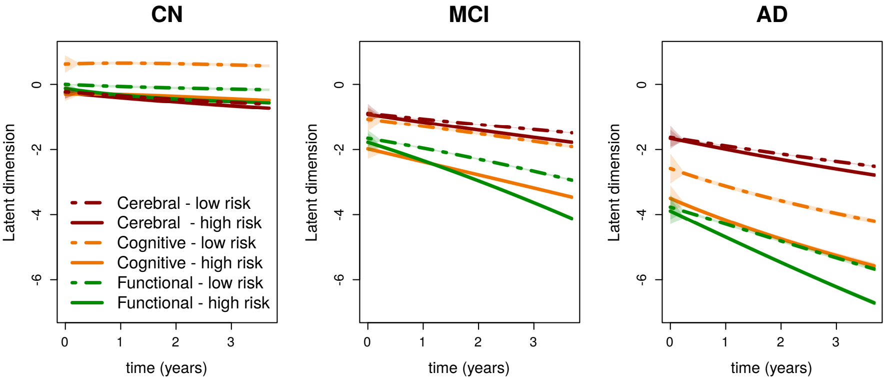
Summary of temporal relationships between dimensions



Significance code: *** < p=0.001 < ** < p=0.010 < * < p=0.050 < · < p=0.100

Predicted trajectories of the dimensions

- Trajectories according to two profiles :
  - high risk (——) : (woman) low educated apoE4 carrier
  - low risk (- – -) : (woman) high educated apoeE4 non-carrier



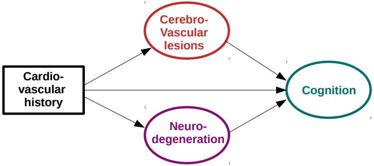
Concluding remarks

- Dynamic modelling of multivariate dimensions :
  - translates local dependence graphs to explore temporal relationships :
    - ★ With latent processes : temporal associations independent of the visit process
    - ★ With fine discretization : numerically feasible method

      causal interpretations not altered with realistically small discretization step
  - relies on equations of difference and multivariate mixed models

    enjoys mixed model properties

- Understanding of temporal associations relevant in many contexts
  - between markers of disease
  - with time-varying exposures
  - in mediation analysis →



- Extensions to other types of data :
  - event history data
  - binary/ordinal/count repeated markers

Funding and References

- Grant SMALA ANR-15-CE37-0002
  Grant DyMES ANR-18-CE36-0004

  Grant France Alzheimer 2018-2020 DataLink

- Methodology detailed in
  - Taddé et al. (2020). Dynamic Modeling of Multivariate Latent Processes and Their Temporal Relationships : Application to Alzheimer's Disease. Biometrics. 2020 ;76 :886–99.
- Program available at
  - https://github.com/bachirtadde/CInLPN
- Other references :

  - Aalen et al (2016). Stat Methods Med Res 25, 2294-314
  - Didelez (2008). JRSS B 70, 245-264
  - Driver & Voelkle (2018). Psychol Methods 23, 774–799
  - Voelkle et al (2018). Multivariate Behav Res 53, 782–805
  - Philipps et al. (2020) on arxiv https://arxiv.org/abs/2009.03840