Joint model with latent state for the pre-diagnosis phase of dementia

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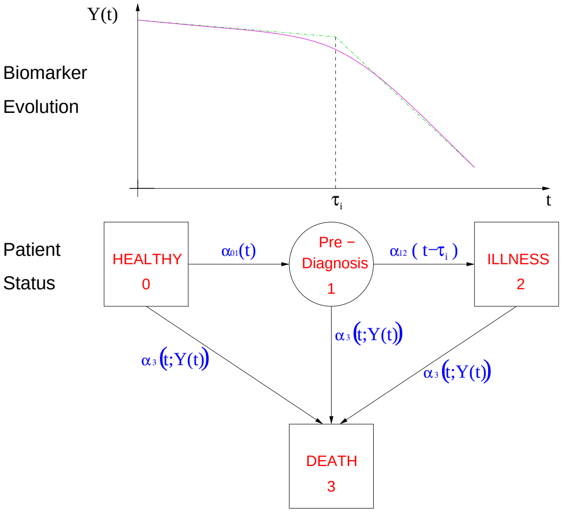
Introduction

- Cognitive evolution is a long-term process beginning before dementia diagnosis :
  - Normal aging associated with a slighter decline
  - Can evolve to an accelerated decline
  - Death is associated with terminal decline
- Subjects go through several states
  - Multi-state models do not allow to describe the time-course of the biomarker
- Joint models for longitudinal evolution and a risk of event do not allow to take into account informative censoring due to death

Objective

- To propose a joint model with latent state for the joint modelling of :
  - quantitative biomarker evolution
  - time-to-dementia
  - time-to-death
- in order to estimate
  - mean trajectories given age at dementia for subjects alive or given age at death
  - age at cognitive decline acceleration
  - duration of the pre-dementia phase

Joint model for the pre-diagnosis phase of dementia



τ_i : age of subject *i* at decline acceleration

Joint model for the pre-diagnosis phase of dementia

Marker Evolution

2 phases linear-linear mixed model rewritten as :

$$Y_{ij} = \beta_{0i} + \beta_{1i}(t_{ij} - \tau_i) + \beta_{2i}(t_{ij} - \tau_i)trn(t_{ij} - \tau_i; \gamma) + \epsilon_{ij}$$

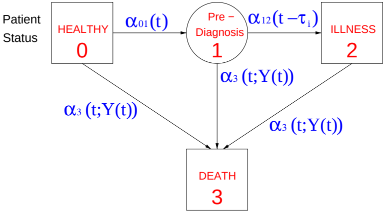
$$\beta_{ki} = \phi_k + \alpha_k' X_{ki} + u_{ki}$$

$$\epsilon_{ij} \sim \mathcal{N}(0, \sigma_\epsilon^2) \qquad u_i \sim \mathcal{N}(0, G) \text{ independent of } \tau_i$$

- β_{0i} : mean biomarker level at τ_i
- β_{1i} : mean of the 2 slopes
- β_{2i} : half difference of the 2 slopes

Joint model for the pre-diagnosis phase of dementia

Multi-State Model



- Latent state transition intensity (state 0 to state 1)

$$\alpha_{01}(t) = \alpha^0_{01}(t)e^{\theta'_\tau X_\tau}$$

- Illness transition intensity (state 1 to state 2)

$$\alpha_{12}(t-\tau_i|u_i) = \alpha^0_{12}(t-\tau_i)e^{\theta'_e X_{ei}+\nu' u_i}$$

- Death transition intensity (to state 3)

$$\alpha_3(t|\tau_i, u_i) = \alpha^0_3(t)e^{\theta'_d X_{di}+\eta\widetilde{Y}_i(t|\tau_i,u_i)}$$

Likelihood

$$
\begin{aligned}
L_i(\theta) &= L_i(Y_i, T_{ei}, \delta_{ei}, T_{di}, \delta_{di}; \theta) \\
&= \int_{-\infty}^{+\infty}\int_{0}^{+\infty} [\mathbb{1}_{\{T_{ei}>\tau_i\}}\alpha_{12}(T_{ei}-\tau_i|u_i)]^{\delta_{ei}} e^{-\mathbb{1}_{\{T_{ei}>\tau_i\}}\Lambda_{12}(T_{ei}-\tau_i|u_i)} \\
&\quad \times \alpha_3(T_{di}|\tau_i,u_i)^{\delta_{di}} e^{-\Lambda_3(T_{di}|\tau_i,u_i)} f_Y(Y_i|\tau_i,u_i) f_\tau(\tau_i) f_u(u_i)\, d\tau_i\, du_i
\end{aligned}
$$

$f_u(u_i)$: multivariate Gaussian density
$f_\tau(\tau_i) = \alpha_{01}(\tau_i)e^{-\Lambda_{01}(\tau_i)}$
$f_Y(Y_i|\tau_i,u_i)$: multivariate Gaussian density

- Left-truncation

$$
l(\theta) = \log \prod_{i=1}^{N} \frac{L_i(Y_i, T_{ei}, \delta_{ei}, T_{di}, \delta_{di}; \theta)}{Pr(T^*_{ei} > T_{0i}, T^*_{di} > T_{0i})}
$$

Estimation

- by a maximum likelihood approach using a Marquardt optimisation algorithm which is a Newton-Raphson like algorithm
- program developped in `Fortran`
- integrals without analytical solutions computed by a Gauss-Hermite quadrature
- positivity constraint for variance parameters and for parameters of baseline intensity functions

PAQUID cohort data on cognitive aging

- 8 visits (V0,V1,V3,V5,V8,V10,V13,V15)
- V0 excluded because first passing effect
- Extracted sample : 2396 subjects with a high education level
- Cognitive score : Benton test measuring the visual memory
- Dementia assessed at each visit
- Cognitive measures collected until dementia or censoring
- Death information obtained in continuous time

Model

Weibull distribution of 2 positive parameters

$$\begin{cases} \alpha_{01}(t) = \lambda_\tau \kappa_\tau (\kappa_\tau t)^{\lambda_\tau - 1} \\ \quad \text{with } \kappa_\tau > 0,\ \lambda_\tau > 0 \\ \alpha_{12}(t - \tau_i) = \lambda_e \kappa_e (\kappa_e (t - \tau_i))^{\lambda_e - 1} \\ \quad \text{with } \kappa_e > 0,\ \lambda_e > 0 \end{cases}$$

Stepwise function of 7 steps every 5 years

$$\begin{cases} \alpha_3(t|\tau_i, u_i) = a_l e^{\eta \widetilde{Y}_i(t|\tau_i, u_i)} \text{ if } T_l \le t < T_{l+1}, l = 1, .., 7 \\ \quad \text{with } a_l > 0,\ T_1 = 65,\ T_2 = 70,\ T_3 = 75, \\ \quad \text{and } T_4 = 80,\ T_5 = 85,\ T_6 = 90 \text{ and } T_7 = 95 \end{cases}$$

Random effects on :

-the biomarker level at τ_i

-the second linear slope

$$\begin{cases} Y_i(t) = \beta_{0i} + \beta_1 (t - \tau_i) + \beta_{2i} \sqrt{(t - \tau_i)^2 + \gamma} + \epsilon_i \\ \quad \text{with } \beta_{0i} = \phi_0 + u_{0i}\ ,\ \ \beta_{1i} = \phi_1 + \frac{u_{s_2 i}}{2} \\ \quad \text{and } \beta_{2i} = \phi_2 + \frac{u_{s_2 i}}{2} \text{ and } \gamma = 0.1 \end{cases}$$

Results

- Mean Benton score at τ_i =10.66 $CI_{95\%}$=[10.51 ; 10.80]
- first slope = -0.073 points by year $CI_{95\%}$=[-0.11 ; -0.038]
- second slope = -0.824 points by year $CI_{95\%}$=[-0.924 ; -0.728]
- Expected age at entry in pre-diagnosis state =86.4 years $CI_{95\%}$=[86.1 ; 86.7]
- Expected transition time between state 1 and state 2 =4.8 $CI_{95\%}$=[4.5 ; 5.2]

Results

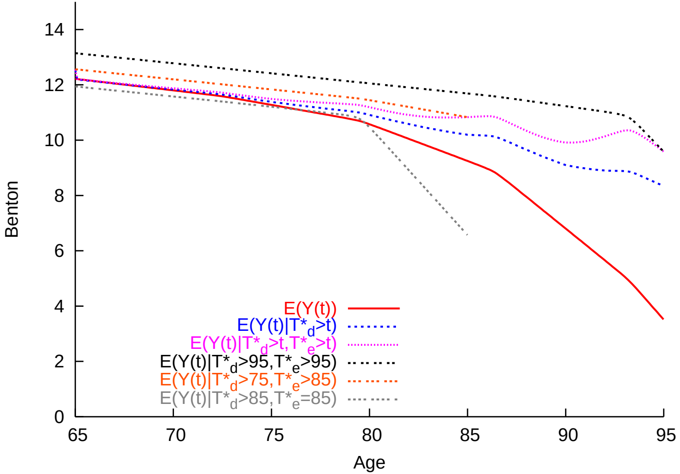


FIG. 1: Marginal mean scores given age (red line) and several mean trajectories given information on dementia age and death age

Results

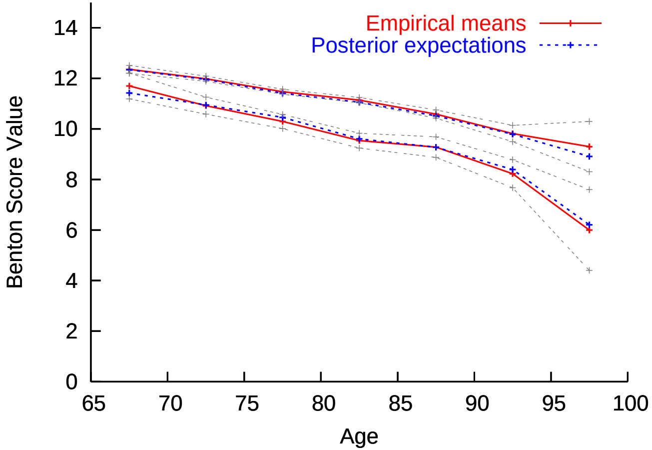


FIG. 2: Posterior evolution compared to empirical evolution for non-demented subjects (upper curve) and demented subjects (lower curve)

Conclusion

- Model advantages :
  - to describe the pre-diagnosis phase of dementia
  - in limiting bias in parameter estimation
  - to give some specific tools for epidemiological interpretation
  - potential application in other chronic diseases with similar data (Cancer, HIV infection,...)
- Model drawbacks :
  - no test of the existence of the pre-diagnosis phase
  - parametric assumptions should be relaxed

References

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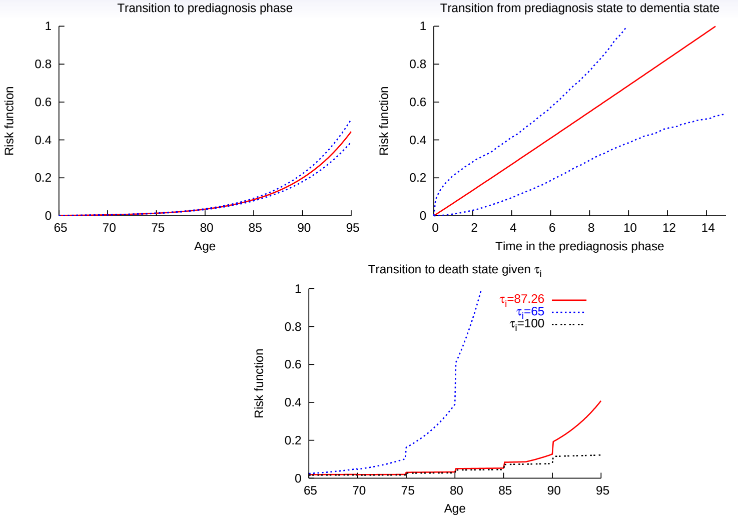

FIG. 3: Instantaneous risk functions for the transitions from state 0 to state 1, from state 1 to state 2 and for death conditionally to τ_i values

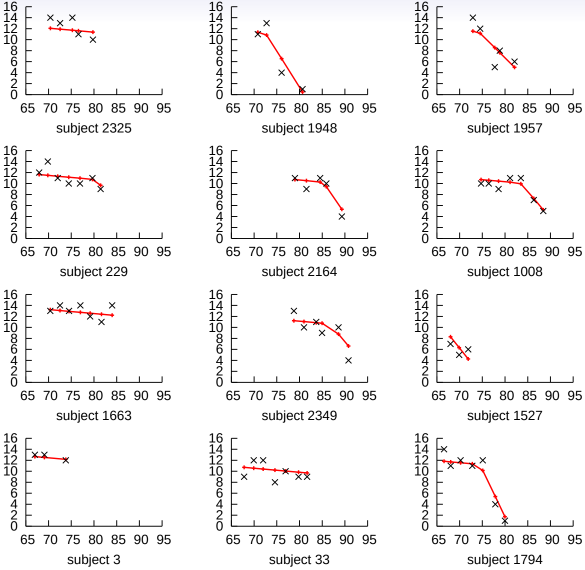

FIG. 4: Individual fit of the Benton Score evolution for 15 subjects

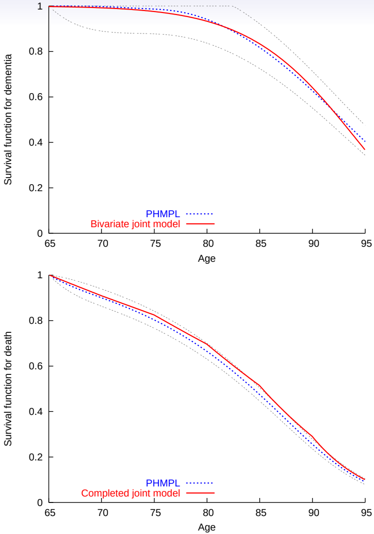

FIG. 5: Marginal survival functions for dementia using the bivariate joint model and for death using the complete joint model compared to corresponding PHMPL survival functions

TAB. 1: Simulations for 100 replications of the joint model of cognitive evolution, dementia and death with a sample of 500 subjects

Parameters	SV	ME	RB(%)	ASE	ESE
ϕ_0	10.66	10.70	0.4	0.125	0.159
ϕ_1	−0.40	−0.37	−6.3	0.026	0.025
ϕ_2	−0.33	−0.31	7.1	0.026	0.025
σ_ϵ	1.55	1.56	0.8	0.028	0.027
$\sqrt{\lambda_e}$	1.38	1.44	4.6	0.121	0.148
$\sqrt{\kappa_e}$	0.46	0.44	−3.3	0.023	0.028
$\sqrt{a_1}$	0.15	0.16	9.6	0.037	0.038
$\sqrt{a_2}$	0.20	0.22	7.6	0.039	0.039
$\sqrt{a_3}$	0.30	0.33	9.4	0.044	0.048
$\sqrt{a_4}$	0.50	0.54	8.8	0.058	0.059
$\sqrt{a_5}$	0.55	0.59	6.6	0.057	0.059
η	−0.17	−0.19	9.5	0.023	0.026
$\sqrt{\lambda_\tau}$	3.98	4.09	2.9	0.072	0.155
$\sqrt{\kappa_\tau}$	0.11	0.11	0.2	0.0001	0.0001
$\sigma_{u_{0i}}$	1.13	1.13	0.3	0.062	0.071

Parameters	CM		BM	
	Estimates	SE	Estimates	SE
ϕ_0	10.656	0.073	10.772	0.071
ϕ_1	-0.448	0.022	-0.364	0.020
ϕ_2	-0.375	0.022	-0.296	0.020
$\sqrt{\lambda_e}$	1.419	0.058	1.417	0.060
$\sqrt{\kappa_e}$	0.429	0.011	0.407	0.011
$\sqrt{a_1}$	0.366	0.044	–	–
$\sqrt{a_2}$	0.355	0.035	–	–
$\sqrt{a_3}$	0.443	0.038	–	–
$\sqrt{a_4}$	0.549	0.043	–	–
$\sqrt{a_5}$	0.690	0.049	–	–
$\sqrt{a_6}$	0.845	0.058	–	–
$\sqrt{a_7}$	0.935	0.073	–	–
η	-0.162	0.015	–	–
$\sqrt{\lambda_\tau}$	3.980	0.040	3.908	0.043
$\sqrt{\kappa_\tau}$	0.106	0.0001	0.106	0.0001
σ_1	1.292	0.040	1.299	0.039
σ_2	0.081	0.046	0.074	0.038
σ_3	0.333	0.032	0.355	0.032