Joint latent class models for longitudinal & survival data in Cancer research

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Progression of Cancers

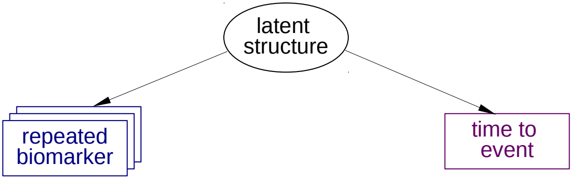
- Progression of cancer studied through:
  - biomarkers (e.g., tumor size, PSA)
  - clinical progression (e.g., recurrence -local,regional,metastatic-, death)

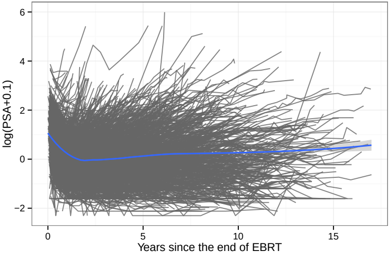
    provide inter-related information that need to be analyzed jointly

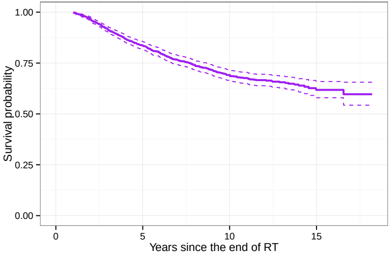
- Joint models useful to address different questions:
  - describe the trajectory of the biomarker stopped by the clinical progression (informative dropout)
  - predict the risk of clinical progression using the biomarker information: adjustment of survival analyses individual dynamic prediction and screening optimization
  - explore/understand the association between the two processes

Joint modelling principle

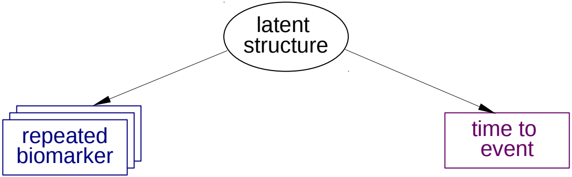
Simultaneous modelling of correlated longitudinal and survival data







Joint modelling approaches



Mixed model
(usually linear)

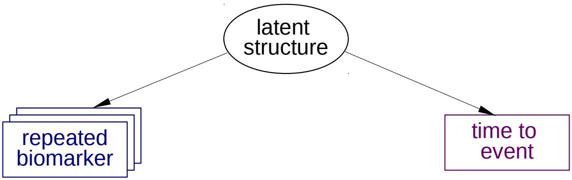
Survival model
(usually proportional hazards)

Link with the latent structure:

- random effects from the mixed model (aka **shared random effect models**)

  → quantifies the effect of the biomarker on the risk of event
  → corrects the biomarker trajectory for the informative truncation by the event

Joint modelling approaches (con't)



Mixed model
(usually linear)

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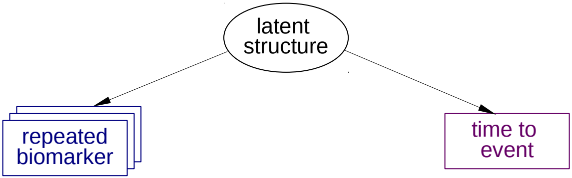
Link with the latent structure:

- latent class structure (aka **joint latent class models**)

  → describes the processes as made of homogenous subgroups
  → more descriptive approach appropriate for *a priori* heterogenous populations

Joint latent class model (JLCM) (Proust-Lima, SMMR 2014)



latent structure

repeated biomarker

time to event

- Shared latent class (c_i) membership:

$$\pi_{ig} = P(c_i = g | X_{pi}) = \frac{e^{\xi_{0g} + X_{Ci}^{\top} \xi_{1g}}}{\sum_{l=1}^{G} e^{\xi_{0l} + X_{Ci} / top \xi_{1l}}} \text{ with } \xi_{0G} = 0 \;\&\; \boldsymbol{\xi_{1G}} = \mathbf{0}$$

- Class-specific linear mixed model for the biomarker trajectory:

$$Y_i(t_{ij}) \;|_{c_i = g} = Z_i(t_{ij})^T b_{ig} + X_{Li}(t_{ij})^{\top} \beta_g + \epsilon_{ij} \text{ with } b_{ig} \sim \mathcal{N}(\mu_g, B_g),\; \epsilon_{ij} \sim \mathcal{N}(0, \sigma_\epsilon^2)$$

- Class-specific proportional hazard model:

$$\lambda(t \mid c_i = g) = \lambda_{0g}(t) e^{X_{Ti}(t) \delta_g}$$

Estimation in the maximum likelihood framework

- Estimation for a fixed number of latent classes G
  - θ_G total vector of parameters

- Individual contribution to the likelihood:
  - *conditional independence given the latent classes*

$$l_i(\theta_G) = \sum_{g=1}^{G} \pi_{ig} f_i(Y_i \mid c_i = g; \theta_G) \lambda_i(T_i \mid c_i = g; \theta_G)^{E_i} S_i(T_i \mid c_i = g, \theta_G)$$

with $S_i(t \mid c_i = g, \theta_G)$ the class-specific survival function

- Multimodality
  - convergence toward local maxima
  - solution: grid search from random initial values

- Software:
  - **Jointlcmm** R function within **lcmm** R package

Selection of the number of classes and posterior classification

- Posterior computations:
  - *posterior* class-membership probability: $\hat{\pi}_{ig}^{Y,T} = P(c_i = g \mid Y_i, (T_i, E_i), X_i; \hat{\theta}_G)$
  - *posterior* classification: $\tilde{c}_i^{Y,T} = argmax_g(\hat{\pi}_{ig}^{Y,T})$

- Number of latent classes to be determined *a posteriori*:
  - Bayesian Information Criterion (BIC)
  - Discriminative performances of the latent classes (e.g., entropy, mean membership probability)
  - Test of conditional independence between Y and T (Jacqmin-Gadda, Bcs 2010)
  - Model fit
  - Size of the classes
  - Clinical question

Not a problem in Bayesian framework with mixtures of Dirichlet process

Illustration in Prostate Cancer (Proust-Lima, SMMR 2014)

- Four patterns of PSA trajectory and risk of any clinical recurrence
  - N=459 men from the University of Michigan Hospital Cohort
  - after a radiation therapy (EBRT)

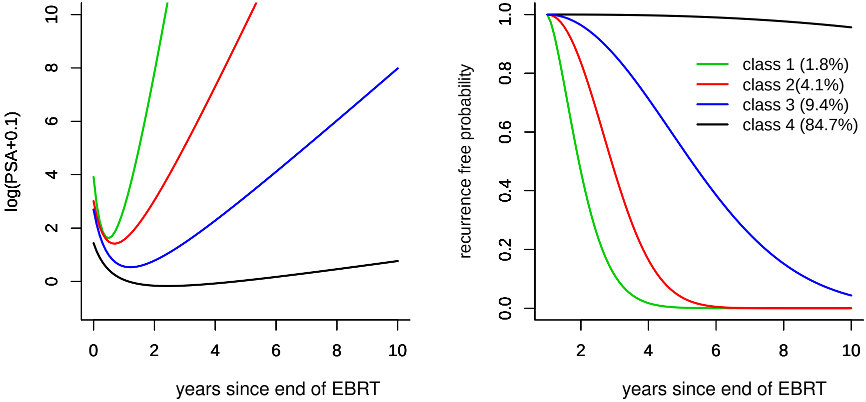
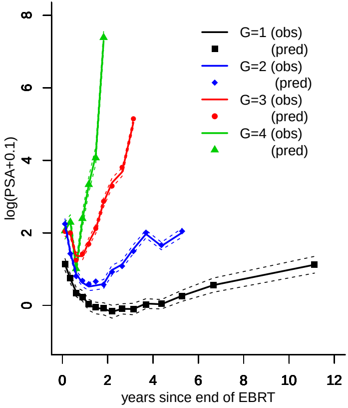


Illustration in Prostate Cancer (Proust-Lima, SMMR 2014)

- Very close to the observations:
  - high discrimination (mean probability of latent class membership $> 92\%$)
  - better than SREM (-400 points in BIC when dependence on level and slope)



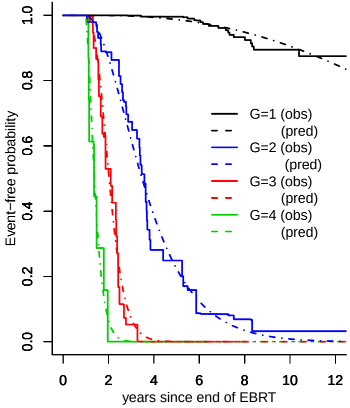


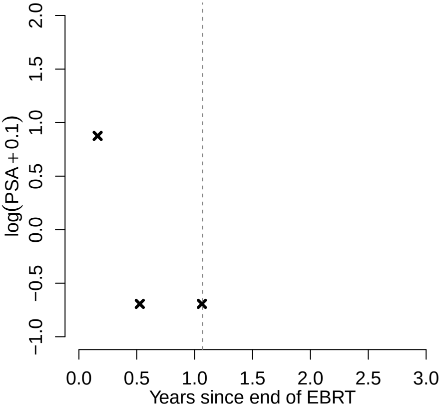
Illustration in Prostate Cancer (Proust-Lima, Biostat 2009, SMMR 2014)

Interesting framework to provide individualized dynamic predictions

- Example for a man with a recurrence at 3.8 years

x PSA measures

Predicted probability
of recurrence
in the next 3 years
with 95%CI:



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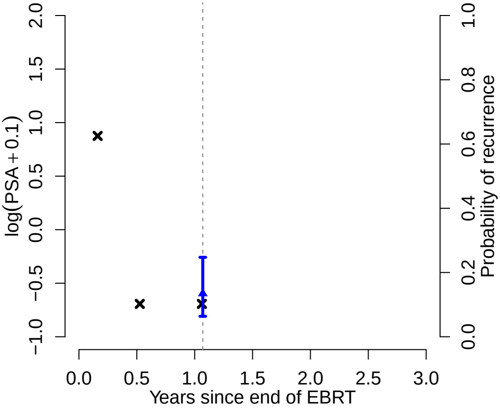

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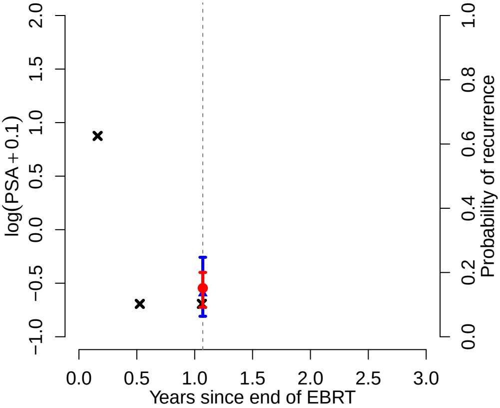

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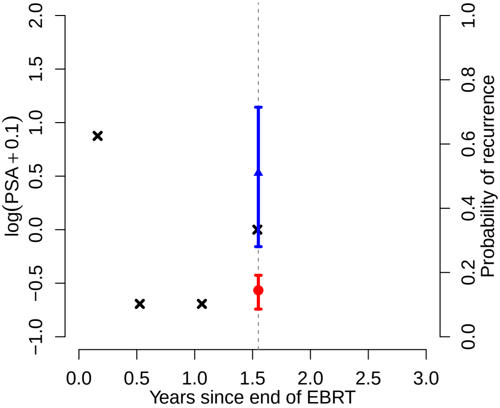

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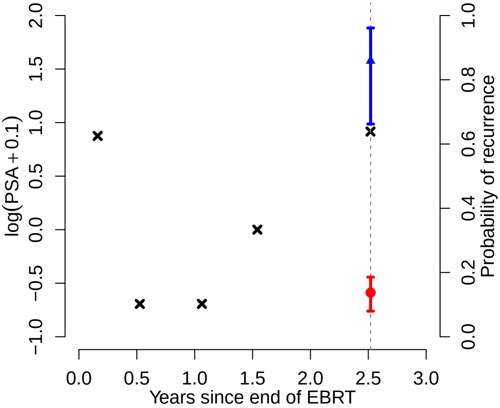
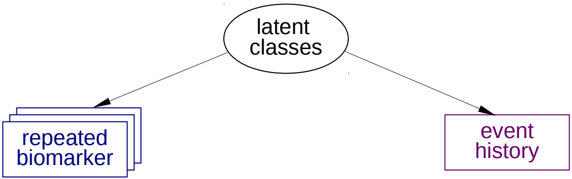


Extensions of joint latent class models



- Competing risk setting
  - cause-and-class specific model (Proust-Lima, Stat Med 2016)
  - ex. first clinical recurrence by type

- multistate data
  - class-specific intensities of transition (Rouanet, Biometrics 2016)
  - ex. whole succession of clinical progressions

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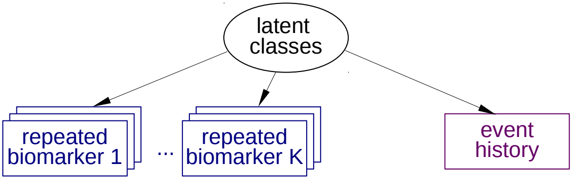

- Multiple biomarkers
  - ex. tumor size and PSA
  - ex. blood marker and toxicity
  - ex. several scales of patient reported outcomes

- Competing risk setting
  - cause-and-class specific model (Proust-Lima, Stat Med 2016)
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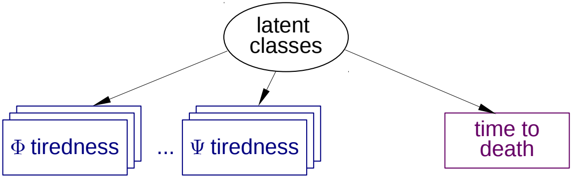
  - ex. whole succession of clinical progressions

Collaboration within French GSO Canceropole

- Observational study in psychology of Health (Institute of Cancer in Montpellier, France)
  - Patients with metastatic colorectal cancer beginning a new cycle of chemotherapy (N=169)
  - Two visual analogue scales of tiredness: **Physical** tiredness and **Psychological** tiredness
  - Measures every 2 weeks for 6 months (n=21 deaths during the follow-up)
- Explore the heterogeneity of trajectories of tiredness
  - Joint latent class model for 2 repeated markers & a censored time to event
    - Latent classes structure central
    - Both markers may be of importance
    - Truncation by death probably informative

Application framework



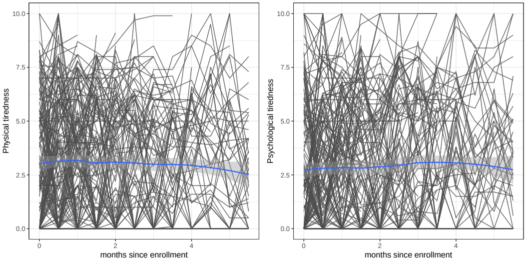
latent classes

Φ tiredness

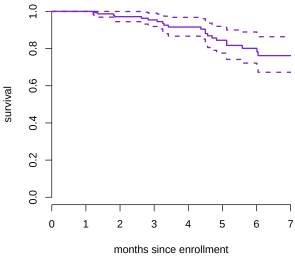
...

Ψ tiredness

time to death



Class-specific quadratic trajectories over time *



Class-specific Weibull risk

Summary of estimated model assuming from 1 to 7 classes

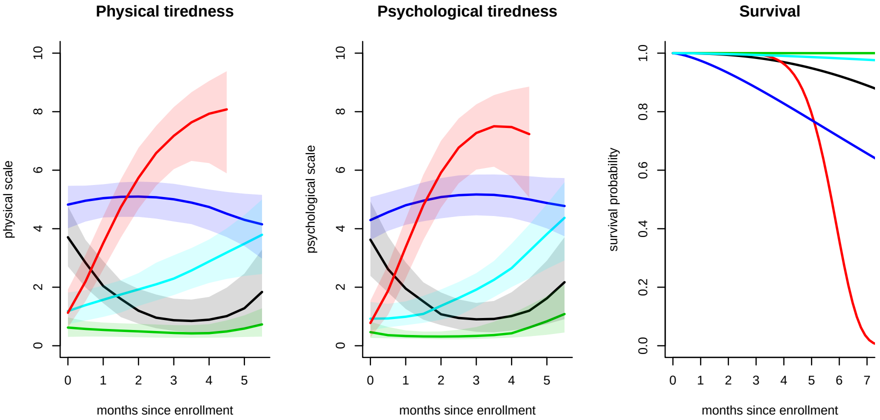
G	p*	log(L)	BIC	E†	Frequency of the latent classes (%)						
					1	2	3	4	5	6	7
1	30	-3642.4	7438.6	1.00	100.0						
2	39	-3562.9	7326.0	0.84	42.6	57.4					
3	48	-3532.0	7310.3	0.82	16.6	42.0	41.4				
4	57	-3502.8	7298.1	0.79	15.4	36.7	14.8	33.1			
5	**66**	**-3473.5**	**7285.6**	**0.81**	**13.0**	**11.2**	**14.8**	**39.1**	**21.9**		
6	75	-3460.6	7306.0	0.80	9.5	18.3	17.8	11.8	20.7	21.9	
7	84	-3449.4	7329.7	0.82	13.6	33.1	8.3	11.8	4.7	20.1	8.3

* number of parameters

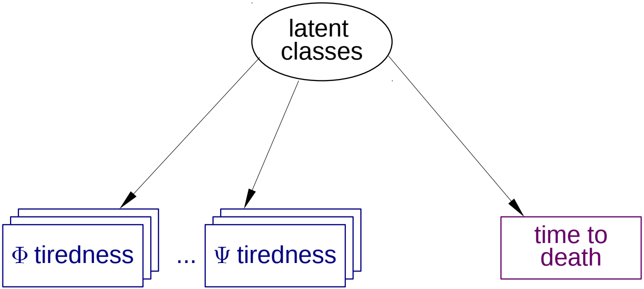
† entropy

- Mean posterior probabilities for G=5: 90%, 86%, 87%, 91%, 84%

Predicted trajectories of tiredness and death



What about a unique process of tiredness?



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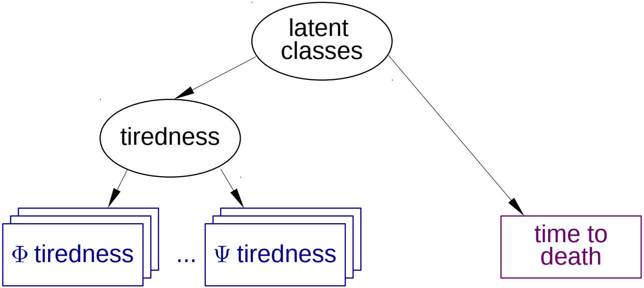
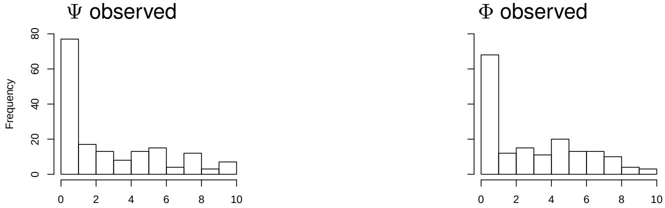


- Changes in the methodology:
  - Class-specific latent class mixed model on the underlying common factor **"tiredness"**
  - Specific equation of observation for each type of observed tiredness scale

What we had to deal with ...

- Non normality of psychological scales (ex. at T=0)



Ψ observed

Φ observed

  - Class-specific linear mixed model

$$Y_{ki}(t_{ij}) \qquad |_{c_i=g} = Z_{ki}(t_{ij})^T b_{kig} + X_{Lki}(t_{ij})^\top \beta_{kg} + \epsilon_{kij}$$

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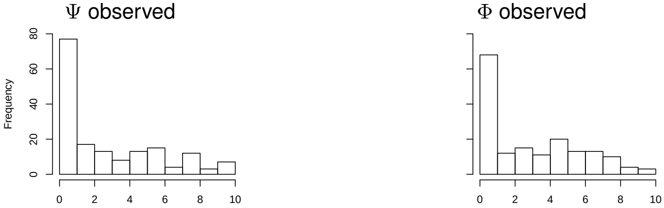

  - Class-specific linear mixed model with a nonlinear link function for each scale k ($k = 1, 2$):

$$H_k(Y_{ki}(t_{ij}); \eta_k) \ |_{c_i=g} = Z_{ki}(t_{ij})^T b_{kig} + X_{Lki}(t_{ij})^\top \beta_{kg} + \epsilon_{kij}$$

with H approximated by cubic I-splines

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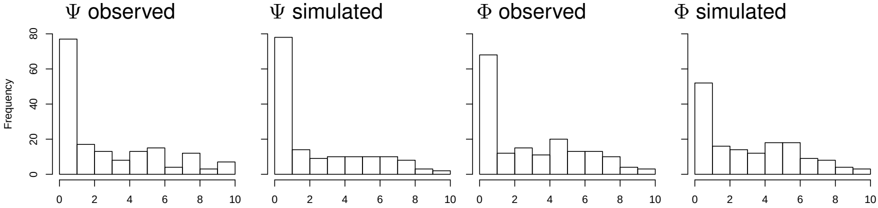

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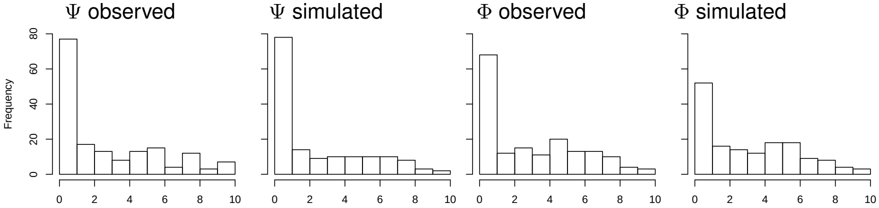

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  - Possible alternatives: class-specific two-part models, class-specific zero-inflated Poisson mixed model (Lévèque, 2018)

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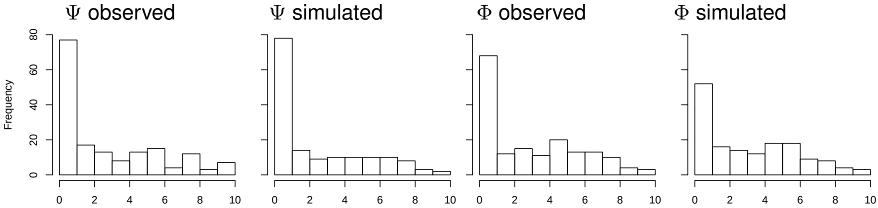

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    with H approximated by cubic I-splines
  - Possible alternatives: class-specific two-part models, class-specific zero-inflated Poisson mixed model (Lévèque, 2018)

- Small number of deaths, other types of dropout

Concluding remarks

- Latent class approach, alternative to shared random effect models
  - not useful to quantify associations
  - relevant to describe trajectories and association with clinical endpoints with less assumptions
  - relevant candidate for individual dynamic predictions

- Same extensions as in SREM (e.g., multivariate Y and T)

- Implemented in R, package `lcmm` (Proust-Lima, JSS 2017)
  - multivariate longitudinal version on github only

- To go further with the methodology?
  - evaluation of the fit to expand (e.g., conditional independence assumption, choice of the number of components)
  - numerical aspects to improve
  - dynamic latent classes (or dynamic stages) migt be more in concordance with disease progression

- Acknowledgement
  - Viviane Philipps: programming and analyses
  - Louise Baussard & Florence Cousson-Gélie: tiredness data collection and scientific question
  - INCA: grants SHS 2015-2018 FATIGUE-TR & SHS 2010-2014 PREDYC

- References
  - Review on JLCM: Proust-Lima et al., SMMR 2014
  - JLCM with multivariate events: Proust-Lima et al., Stat Med 2016 ; Rouanet et al., Biometrics 2016
  - Evaluation: Jacqmin-Gadda et al., Biometrics 2010
  - Individual dynamic predictions: Proust-Lima and Taylor, Biostatistics 2009
  - R package: Proust-Lima, Philipps, Liquet, J Stat Software 2017
    `https://github.com/CecileProust-Lima/lcmm`