Modélisation conjointe de données longitudinales et de temps d'événements sous R

Joint modeling of longitudinal and time-to-event data in R

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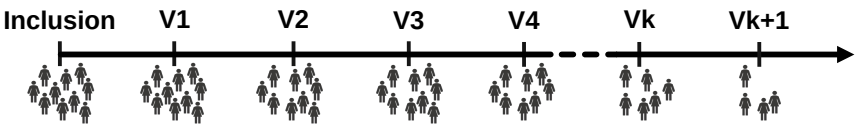
Epidemiological studies

- Overal cohort design:

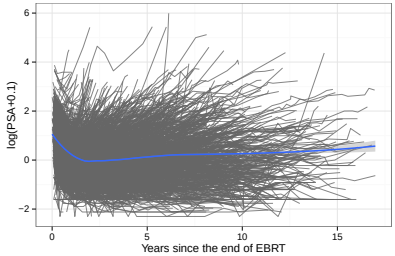


- Target population:
  - Whole population in a certain window of age
    - ★ 3-City Study: elderly - ELFE: young children - CONSTANCES: adults
  - Population with a certain diagnosis (e.g., cancer, Multiple System Atrophy)
    - ★ Clinical prospective cohort: monitoring the population for prognosis
    - ★ Clinical trial: testing an intervention in randomized groups

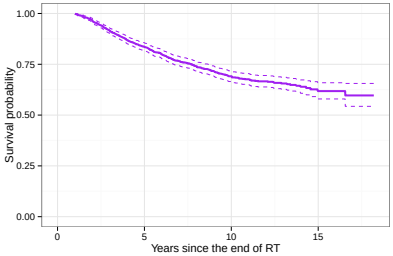
- Available data
  - at baseline (exposures, confounders, participant characteristics)
  - over follow-up (exposures, health indicators, events)

Progression of health phenomena studied through

- repeated measures of marker (e.g., blood biomarker, MRI features, PRO / QoL scales) or exposure (e.g., blood pressure, BMI)



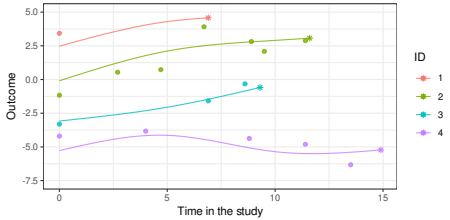
- time to health outcome (e.g., death, diagnosis, progression, dropout)



provide inter-related information that need to be analyzed together (jointly)

The endogenous nature of time-varying variables

- Marker/Exposure data are **measures of an underlying process**:
  - measured with error
  - measured at sparse and irregular times
  - influenced by the event occurence: endogenous / internal



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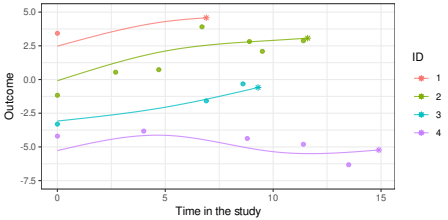


- Dedicated biostatistical model = **mixed models / random-effect models**

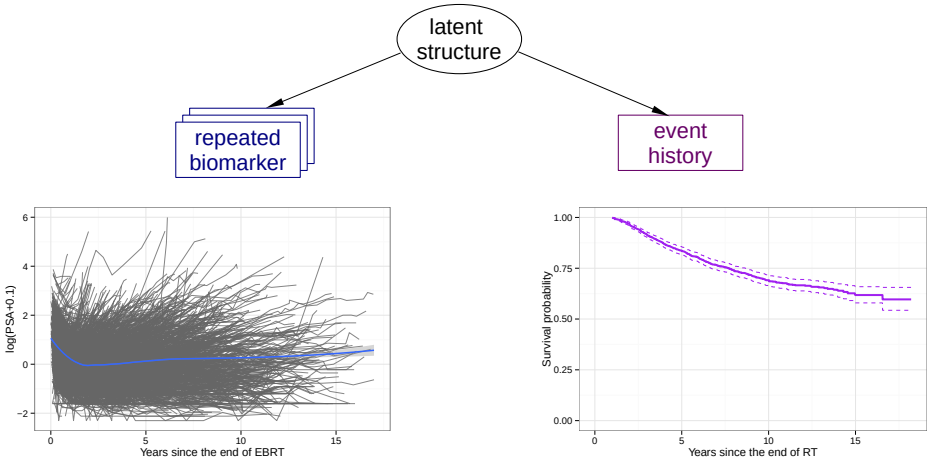
- Underlying process of interest $Y^*(t)$ defined at any time $t \in \mathbb{R}$

$$Y_i^*(t) = \boldsymbol{X}_i(t)^\top \boldsymbol{\beta} + \boldsymbol{Z}_i(t)^\top \boldsymbol{b}_i \quad \text{with} \quad \boldsymbol{b}_i \sim \mathcal{N}(0, \boldsymbol{B})$$

- Observations Y_{ij} at sparse times t_{ij}
  - ★ with generally truncation at the event time: $\max(t_{ij}) < T_i$
  - ★ with random measurement error: $Y_{ij} = Y_i^*(t_{ij}) + \varepsilon_{ij}$ with $\varepsilon_{ij} \underset{iid}{\sim} \mathcal{D}$

- Estimation in R:
  lme (nlme),
  lmer (lme4),
  hlme (lcmm),
  ...

Joint modelling principle



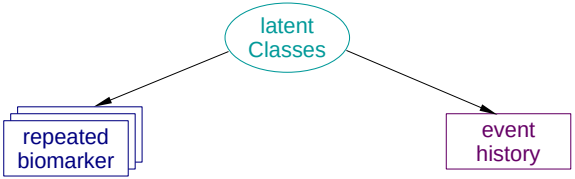
Simultaneous modelling of correlated longitudinal and survival data

(Classical) Research Questions addressed by joint models

- quantify the association of a endogenous marker with the risk of event
- predict the risk of clinical endpoint using the biomarker information
  - individual dynamic prediction and screening optimization
- describe the trajectory of the biomarker stopped by the clinical progression
  - and evaluate its determinants
- explore/understand the association between the two processes
  - variability / heterogeneity in the disease progression

Joint latent class models (JLCM) (Proust-Lima, 2014)

- Latent class c_i: $P(c_i = g) = \pi_{ig} = \frac{e^{\xi_{0g} + X_{Ci}{}^\top \xi_{1g}}}{\sum_{l=1}^{G} e^{\xi_{0l} + X_{Ci}{}^\top \xi_{1l}}}$ (with $\xi_{0G} = 0$ & $\xi_{1G} = \mathbf{0}$)



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

$$\begin{aligned} Y_{ij}|_{c_i=g} &= Y_{ig}^*(t_{ij}) + \epsilon_{ij} \\ &= Z_i(t_{ij})^T b_i|_{c_i=g} + X_{Li}(t_{ij})^\top \beta_g + \epsilon_{ij} \\ b_i|_{c_i=g} &\sim \mathcal{N}(\mu_g, B_g),\ \epsilon_{ij} \sim \mathcal{N}(0, \sigma_\epsilon^2) \end{aligned}$$

- proportional hazard model for the event:

$$\lambda_i(t \mid c_i = g) = \lambda_{0g}(t) \exp(X_{Ti}(t)\delta_g)$$

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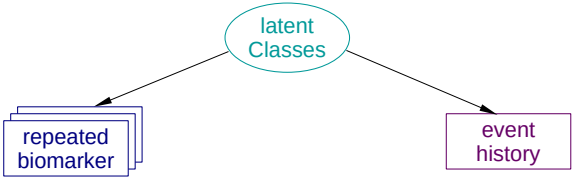

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- proportional hazard model for the event:

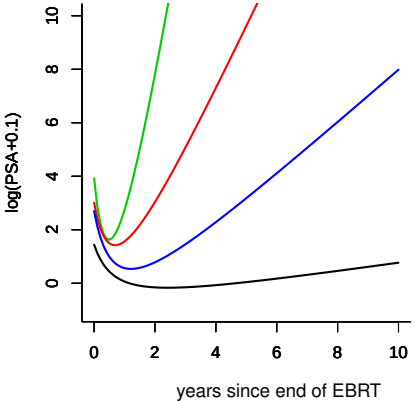
$$\lambda_i(t \mid c_i = g) = \lambda_{0g}(t) \exp(X_{Ti}(t)\delta_g)$$

→ describes the processes as made of homogenous subgroups

→ descriptive approach appropriate for *a priori* heterogenous populations

JLCM 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)



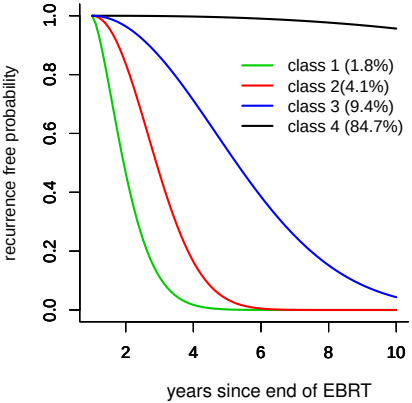
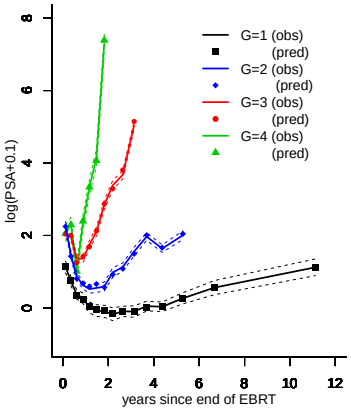
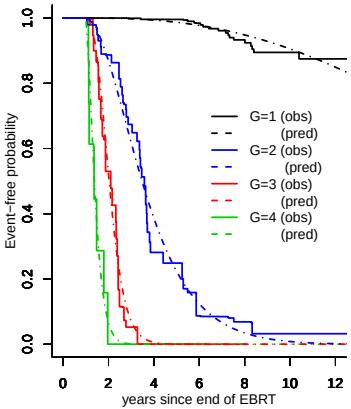


Illustration in Prostate Cancer (Proust-Lima, SMMR 2014)

- Very close to the observations:
  - high discrimination (mean probability of latent class membership > 92%)
  - excellent fit to the data compared to other joint models





Estimation in lcmm R package (Proust-Lima, JSS 2017)

- Maximum Likelihood Estimates

$$\mathscr{L}_i(\boldsymbol{\theta}) = \sum_{g=1}^{G} f(Y_i \mid c_i = g; \boldsymbol{\theta}) \;\; f(T_i \mid c_i = g; \boldsymbol{\theta}) \;\; P(c_i = g; \boldsymbol{\theta})$$

- Optimization algorithm: Marquardt-Levenberg Algorithm with marqLevAlg R package (Philipps R Journal 2022)
  - Newton-like optimization
  - Strict convergence criteria (parameter stability, likelihood stability, first and second derivatives)
  - Parallel numerical computations of the derivatives

- Management of local maxima
  - Grid search = B estimations from random initial values

- Variance-covariance matrix given by the inverse of the Hessian matrix

lcmm in practice: jlcmm or Jointlcmm function

```
 # G=1
m1 <- jlcmm( fixed = logPSA ~ I((time + 1)^(-1.5)) + time,
             random =~ I((time + 1) ^(-1.5)) + time, subject = "ID",
             survival = Surv(tsurv,event) ~ tstage2 + tstage34,
             hazard = "splines",
             data = cohort)


 # G=4
m4 <-
     jlcmm( fixed = logPSA ~ I((time + 1)^(-1.5)) + time,
             random =~ I((time + 1) ^(-1.5)) + time, subject="ID",
             mixture =~ I((time + 1)^(-1.5)) + time,
             survival = Surv(tsurv,event) ~ tstage2 + tstage34,
             hazard = "splines", hazardtype = "PH",
             ng = 4, data = cohort, B = random(m1))
```

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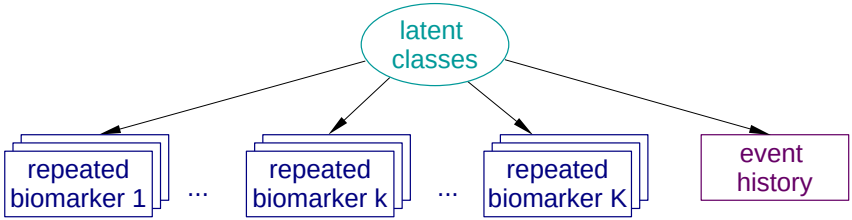
 # G=4
m4 <- gridsearch(
      jlcmm( fixed = logPSA ~ I((time + 1)^(-1.5)) + time,
             random =~ I((time + 1) ^(-1.5)) + time, subject="ID",
             mixture =~ I((time + 1)^(-1.5)) + time,
             survival = Surv(tsurv,event) ~ tstage2 + tstage34,
             hazard = "splines", hazardtype = "PH",
             ng = 4, data = cohort,
             rep = 100, maxiter = 30, minit = m1, cl = 10)
```

Extensions to more complex data structure: longitudinal / competing causes

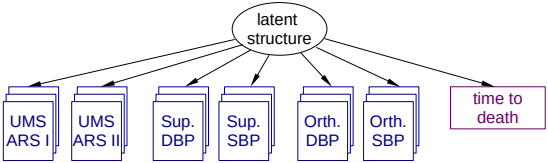


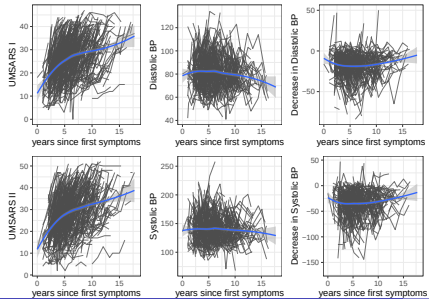
Class-and-marker-specific mixed model
(Proust-Lima, Stat Med 2023)

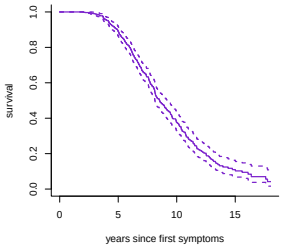
cause-and-class proportional hazard model
(Proust-Lima, Stat Med 2016)

- estimation in R: mpjlcmm function in package lcmm

Example in Multiple System Atrophy (MSA)







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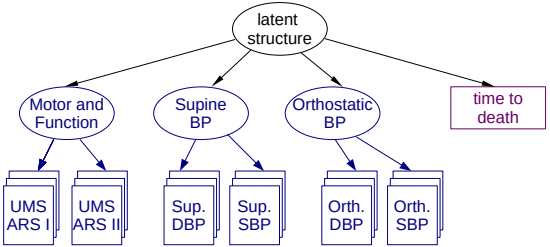
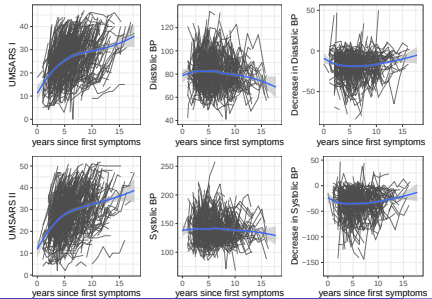
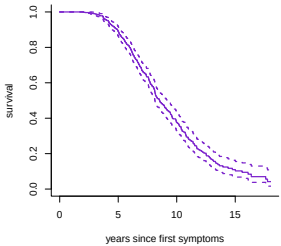




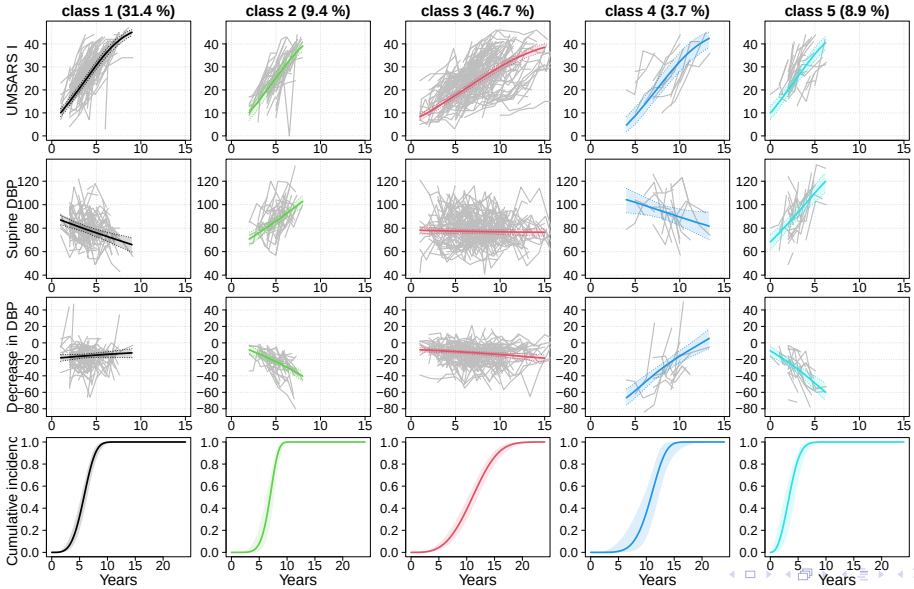


Actual structure of mpjlcmm R function

(Proust-Lima, Stat Med 2023)

- Latent process mixed model with latent classes
- Marker-specific measurement model

5 latent classes identified



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$$\lambda_i(t) = \lambda_0(t) \exp(Y^*(t)\boldsymbol{\eta})$$

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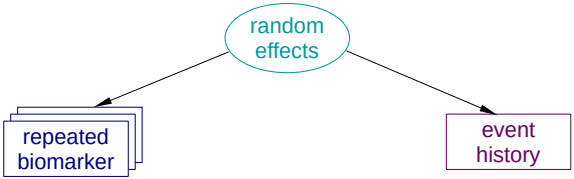
Shared Random-Effect Models (SREM) (Rizopoulos, 2012)

- Shared random-effects b_i distribution:

$$\boldsymbol{b}_i \sim \mathcal{N}(0, \boldsymbol{B})$$



- linear mixed model for the biomarker trajectory:

$$\begin{aligned} Y_{ij} \,|\boldsymbol{b}_i &= Y_i^*(t_{ij}) + \epsilon_{ij} \\ &= \boldsymbol{X}_{Li}(t_{ij})^\top \boldsymbol{\beta} \;+\; \boldsymbol{Z}_i(t_{ij})^\top \boldsymbol{b}_i \;+\; \epsilon_{ij} \quad \epsilon_{ij} \sim \mathcal{N}(0, \sigma_\epsilon^2) \end{aligned}$$

- proportional hazard model for the event:

$$\lambda_i(t; \boldsymbol{b}_i) = \lambda_0(t) \exp\left(\boldsymbol{X}_{Ti}(t)^\top \boldsymbol{\delta} + \; Y_i^*(t)\; \eta\right)$$

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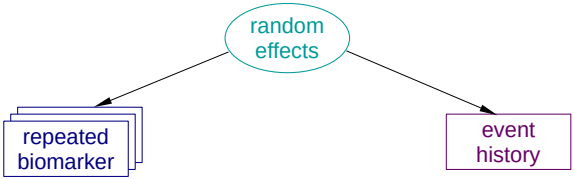

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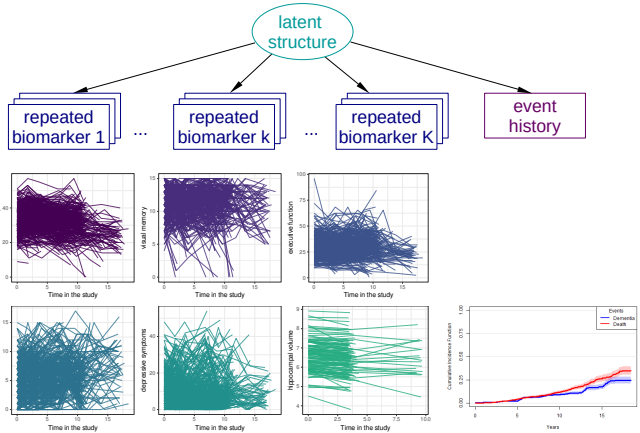
$$\lambda_i(t; \boldsymbol{b}_i) = \lambda_0(t) \exp\left(\boldsymbol{X}_{Ti}(t)^\top \boldsymbol{\delta} + \boldsymbol{f}\ (t, \boldsymbol{b}_i, ...)\ \boldsymbol{\eta}\right)$$

→ $\boldsymbol{\eta}$ quantifies the effect of the biomarker on the risk of event

→ biomarker trajectory corrected for the informative truncation by the event

Joint models with multivariate longitudinal / survival data



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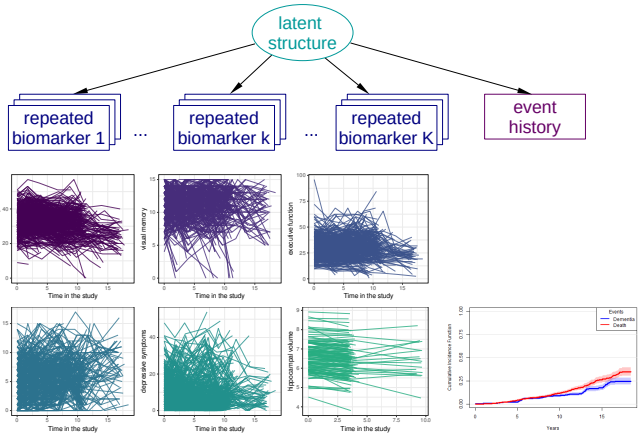

- K different linear mixed models
  - a big vector of random effects: $\boldsymbol{b}_i = (\boldsymbol{b}_{i1}, ..., \boldsymbol{b}_{ik}, ..., \boldsymbol{b}_{iK})$
- P cause-specific survival models

$$\lambda_{ip}(t; \boldsymbol{b}_i) = \lambda_{0p}(t) \times \exp\left(\boldsymbol{X}_{Ti}(t)\delta_p + \sum_{k=1}^{K} \boldsymbol{f}_k(t, \boldsymbol{b}_{ik}, ...)\, \boldsymbol{\eta}_{kp}\right)$$

- Examples:
  - Effect of a marker/exposure adjusted for other time-varying variables
  - Prediction of the event based on all the information available

Estimation in R (not exhaustive list!)

	inference	algorithm	integration	distributions	multiple markers
JM	Freq	EM/optim/MLA	paGH	Gaussian	✗
JMbayes	Bayes	MCMC		Exp. family	✓
JMbayes2	Bayes	MCMC		Exp. family	✓
joineR	Freq	EM	GH	Gaussian	✗
joineRML	Freq	MCEM	qMC	Gaussian	✓
rstanArm	Bayes	STAN		Exp. Family	✓
INLAJoint	Bayes	INLA		Gauss. process	✓
JLPM	Freq	MLA	qMC	Bin/ord/curvi	✗ /✓
frailtyPack	Freq	MLA	aGH	Gaussian	✗
JMBordo	Freq	MLA	qMC	Exp. Family	✓
... and saemix, BeQut and others ...					

qMC = quasi Monte Carlo; (p)aGH = (pseudo) adaptive Gauss Hermite

→ **Various specifications:** mixed models, survival models, dependence structure, data nature, ...

Example with JMbayes2

Structure common to packages of Rizopoulos's group : JM, JMbayes, JMbayes2

```
library("JMbayes2")
# specification of the longitudinal model(s)
LongModel <- lme(log(serBilir) ~ year * sex, data = pbc2, random = ~ year | id)

# specification of the survival model
CoxModel <- coxph(Surv(years, status2) ~ sex, data = pbc2.id)

# estimation of the joint model (by default, current value)
jointFit1 <- jm(CoxModel, LongModel, time_var = "year")
```

Numerical issues in SREM with multiple longitudinal biomarkers

1. Log-likelihood computation becomes rapidly untractable (huge numerical integration)

$$\mathscr{L}_i(\boldsymbol{\theta}) = \int_{\boldsymbol{b_i}} f(Y_i \mid \boldsymbol{b_i}; \boldsymbol{\theta}) \; f(T_i \mid \boldsymbol{b_i}; \boldsymbol{\theta}) \; f(\boldsymbol{b_i}; \boldsymbol{\theta}) \; d\boldsymbol{b_i}$$

Solutions:

- (quasi) Monte Carlo integration
- Bayesian inference (e.g., MCMC, INLA)

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2. Large number of predictors in the survival model with $\sum_{k=1}^{K} \boldsymbol{f}_k\ (\ t, \boldsymbol{b}_{ik}, ...)\ \boldsymbol{\eta}_{kp}$

   Solutions:
   - Regularization in the survival model - Lasso - (e.g., Andrinopoulou and Rizopoulos SiM 2012, Chen and Wang SiM 2017)

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   Solutions:
   - 2-step methods / regression calibration (Ye et al., 2008, Signorelli et al., 2021, Mauff et al. 2020)

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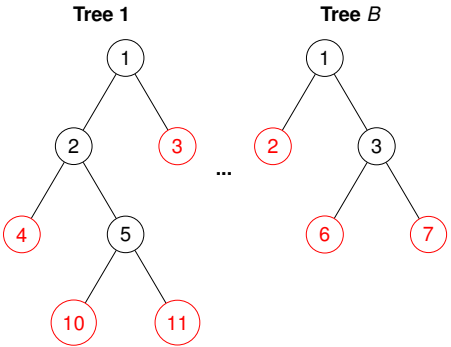
What about totally changing the framework and use random forests?

Random survival forests for competing causes of events

- Random survival forest principle (Ishwaran et al. 2008, 2014)
  - Ensemble of decision trees that partition the subjects into homogeneous leaves regarding survival



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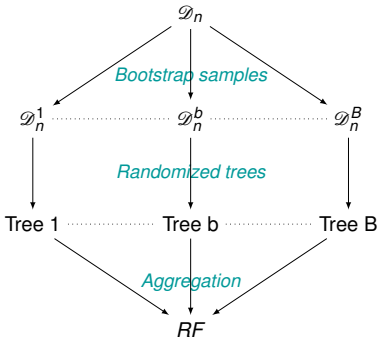

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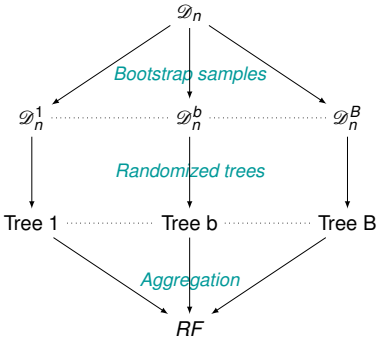
  - Handle complex relationship between predictors and event

- Cons:
  - ⚠ Limited to time-independent predictors



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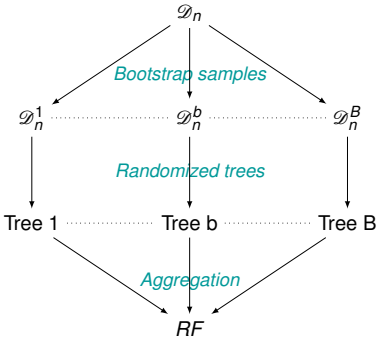
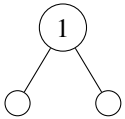


- Our solution: **DynForest**
  - Incorporate time-dependent predictors in the tree building process

Splitting rule in random survival forests

Find two groups of subjects which maximize the difference in event probability:

1. Randomly draw `mtry` predictors
2. Build two groups from each predictor's values
3. Compute the statistic to quantify the distance (e.g. Fine & Gray for the event probability)



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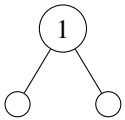

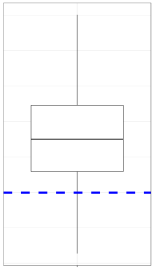

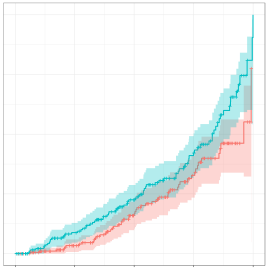

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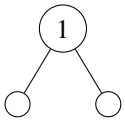

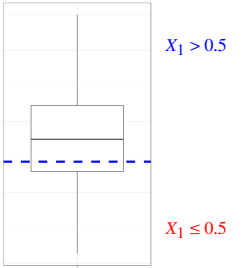

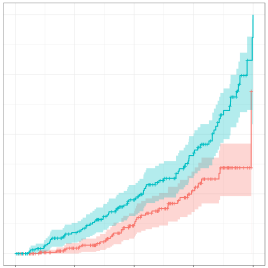

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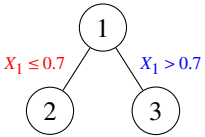
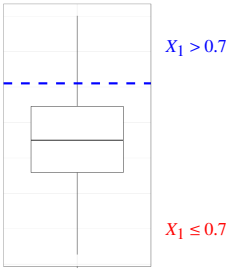
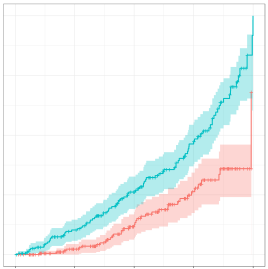




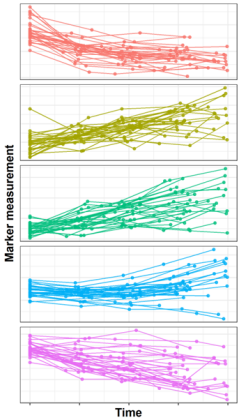


How to incorporate time-dependent predictors?

At each node, transform time-dependent predictors Y_k into time-fixed features :

1. Model $\boldsymbol{Y}_k$ trajectory using mixed models:

$$Y_{ik}(t_{ijk}) = \boldsymbol{Z}_{ik}(t_{ijk})^\top(\boldsymbol{\beta}_k + \boldsymbol{b}_{ik}) + \epsilon_{ijk}$$



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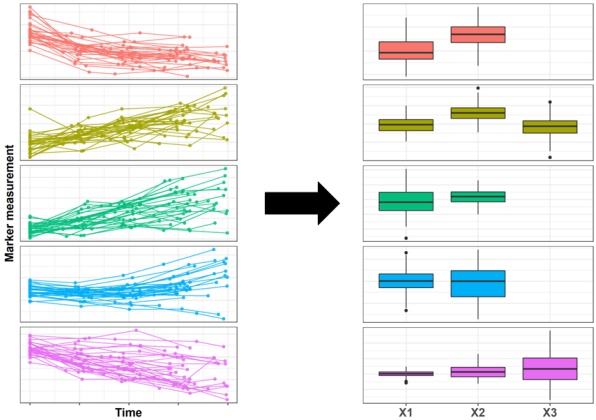
$$\hat{\boldsymbol{b}}_{ik} = \mathbb{E}(\boldsymbol{b}_{ik}|\boldsymbol{Y}_i)$$



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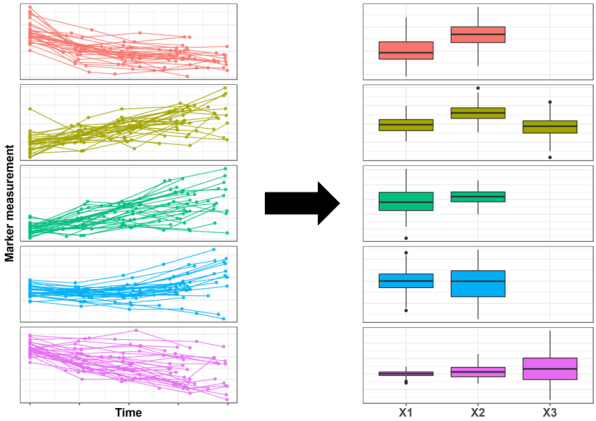
3. Consider them as splitting variable candidates

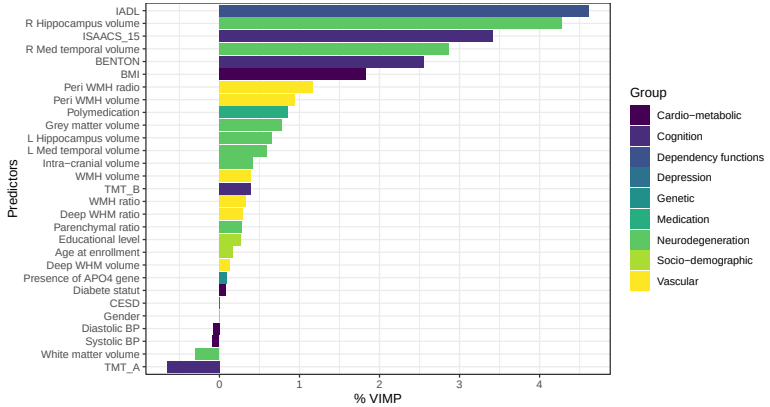


DynForest in practice: example of call

```r
library(DynForest)

# definitions of the objects:
Y <- list(type = "surv", Y = unique(pbc2_train[,c("id","years","event")]))
fixedData_train <- unique(pbc2_train[,c("id","age","drug","sex")])
timeData_train <- pbc2_train[,c("id","time","serBilir","SGOT","albumin","alkaline")]

# definitions of mixed models:
timeVarModel <- list(serBilir = list(fixed = serBilir ~ time, random = ~ time),
                     SGOT = list(fixed = SGOT ~ time + I(time^2), random = ~ time + I(time^2)),
                     albumin = list(fixed = albumin ~ time, random = ~ time),
                     alkaline = list(fixed = alkaline ~ time,random = ~ time))

# training of the forest:
res_dyn <- DynForest(timeData = timeData_train,
                     fixedData = fixedData_train,
                     timeVar = "time", idVar = "id",
                     timeVarModel = timeVarModel, Y = Y,
                     ntree = 200, mtry = 3, nodesize = 2, minsplit = 3,
                     cause = 2, ncores = 7, seed = 1234)
```

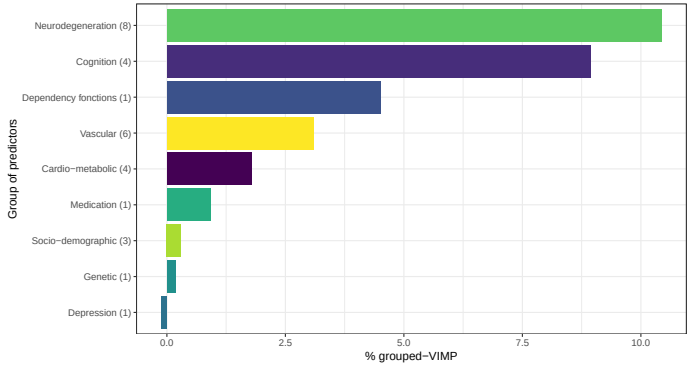
Application to dementia from multi-modal repeated data in 3C

Quantification of the variable importances for the prediction: 24 time-dependent predictors, 5 time-fixed predictors



Application to dementia from multi-modal repeated data (by groups

Quantification of the variable importances for the prediction **by group**



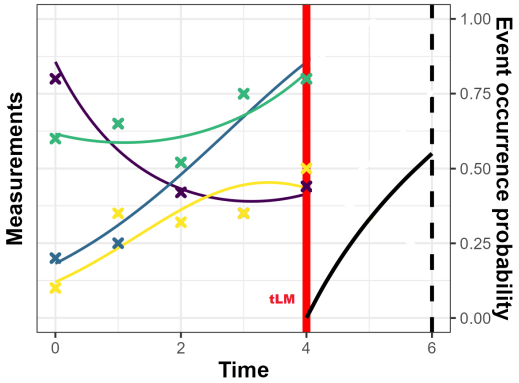
(Classical) Research Questions addressed by joint models

- quantify the association of a endogenous marker with the risk of event
- predict the risk of clinical endpoint using the biomarker information
  - individual dynamic prediction and screening optimization
- describe the trajectory of the biomarker stopped by the clinical progression
  - and evaluate its determinants
- explore/understand the association between the two processes
  - variability / heterogeneity in the disease progression

Dynamic prediction for a new subject ⋆

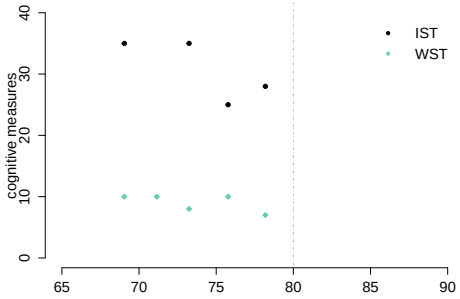
- Predicted probability from landmark s at horizon t:

$$\pi^{\star}(s,t) = \mathbb{P}\left(T_{\star} < s+t, \delta_{\star} = p | T_{\star} > s, \mathscr{Y}_{\star}(s), \mathscr{X}_{\star}\right)$$



Dynamic prediction for a new subject $\star$: joint models

- Direct posterior computation (Bayes):
  - Monte Carlo approximation of the posterior distribution
  - e.g. with **`dynpred`** function in lcmm, with **`predict`** function in JMbayes2
- Performances evaluation:
  - **`riskRegression`** R package for AUC, Brier Score (Gerds & Kattan, 2021; Blanche, 2015)
  - in lcmm, **`epoce`** function for UACV (Commenges, Bcs 2011)



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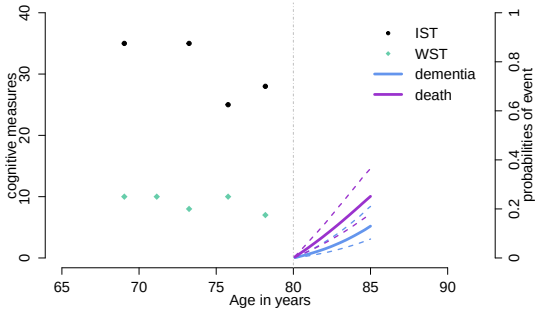

	at 80 years old
5-year probability of dementia (%):	13.0 [7.7,21.0]
5-year probability of death (%) :	25.1 [18.1,36.5]

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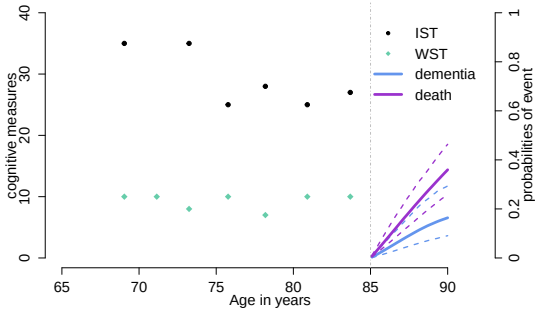


	at 80 years old	at 85 years old
5-year probability of dementia (%):	13.0 [7.7,21.0]	16.4 [9.1,29.4]
5-year probability of death (%) :	25.1 [18.1,36.5]	36.0 [25.9,46.3]

Dynamic prediction for a new subject $\star$: random forests

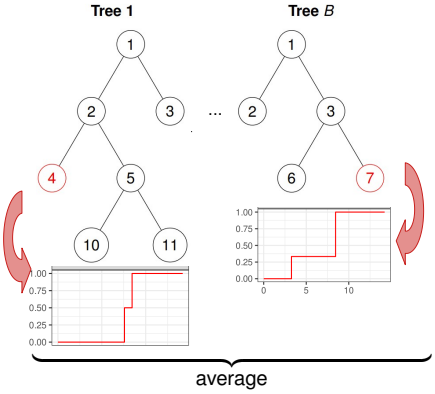
- Predicted probability from landmark s at horizon t:

$$\pi^{\star}(s,t) = \mathbb{P}\left(T_{\star} < s+t, \delta_{\star} = p | T_{\star} > s, \mathscr{Y}_{\star}(s), \mathscr{X}_{\star}\right)$$

- Drop down the new subject $\star$ into the trees using:
  - the history of time-dependent predictors $\mathscr{Y}_{\star}(s)$ up to landmark time s
  - time-fixed covariates $\mathscr{X}_{\star}$

- Average the leaf-and-tree-specific cumulative incidence functions $\hat{\pi}^{(tree,leaf)}(s,t)$ across trees:

$$\hat{\pi}_{\star}(s,t) = \frac{1}{B}\left(\hat{\pi}_{\star}^{(1,4)}(s,t) + ... + \hat{\pi}_{\star}^{(B,7)}(s,t)\right)$$



Concluding remarks

- Joint models = central technique in health studies (and probably beyond)
  - understanding of etiology, natural history and progression
  - individual dynamic prediction
  - correct for informative dropout

- Different solutions/implementations available in R
  - latent classes /shared random effects
  - different parametric assumptions (baseline risk, distribution of outcomes)
  - numerical limitations with many longitudinal markers

- `DynForest`: example of promising alternative from statistical learning
  - Not a two-step approach!
    - ★ separate mixed models for the longitudinal markers at each node
    - ★ naturally handles informative censoring of biomarker data as estimated on homogeneous nodes
  - accounts for nonlinear associations, interactions, etc.
  - current extensions with FPCA tools (Segalas 2024), distances, and other splitting rules

- Fundings:

Réseau de Recherche Impulsion
PHDS | Public Health Data Science
Bordeaux Network
Université de BORDEAUX

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