

Joint model with latent disease age
Overcoming the need for reference time

J. ORTHOLAND, S. DURRLEMAN, S. TEZENAS DU MONTCEL

Preliminary results that need to be consolidate

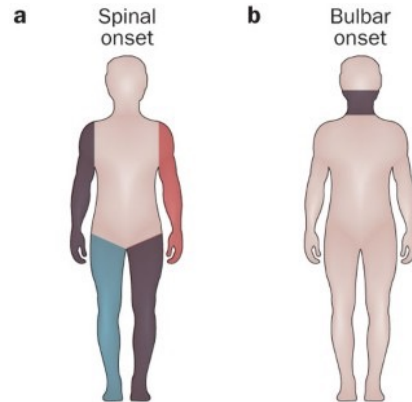
A rare chronic disease 1-2.6 cases per 100 000 persons annually [Talbot, 2016]

No cure...

...due to challenges

Riluzole prolonged survival by approximately four months [Traynor, 2003]

Heterogeneity



No clear starting point

BMI decreases years before symptom onsets [Peter, 2017]

Modelling could help explain the heterogeneity

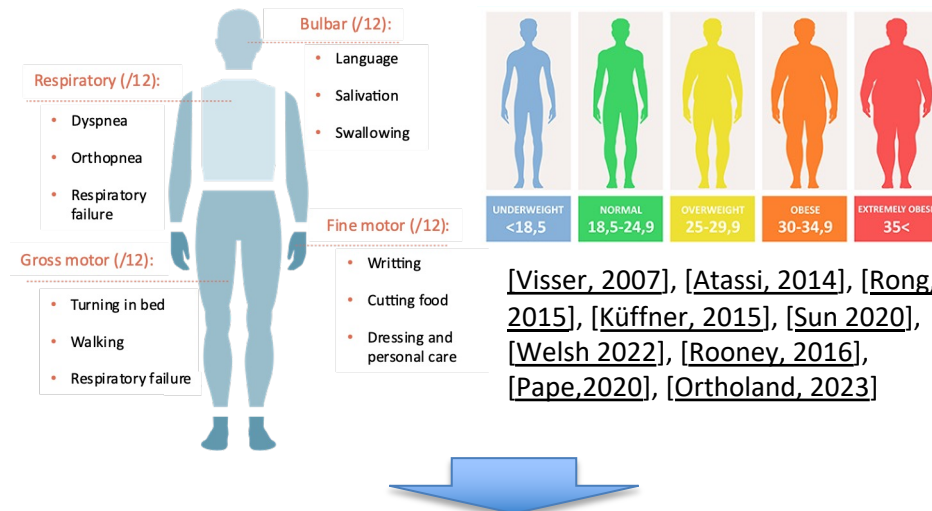
Average survival from onset to death is 3-4 years [Talbot, 2016]

[Haverkamp, 1995], [Jablecki, 1989],
 [Pape,2020], [Trosji,2020], (Norris, 1993),
 [Murdock, 2021], [Tortelli, 2014], [Visser,
 2007], [Atassi, 2014], [Elamin 2015], [Reniers
 2017], [Hesters 2020], [Sun 2020]



Survival models:

- Kaplan Meyer [Kaplan, Meier, 1958],
- AFT [Kalbfleisch, 2002],
- Cox model [Cox, 1972].



Longitudinal models:

- GLM [McCulloch, 2008]: need for a reference time,
- Non-linear mixed effect model [Schiratti, 2015]

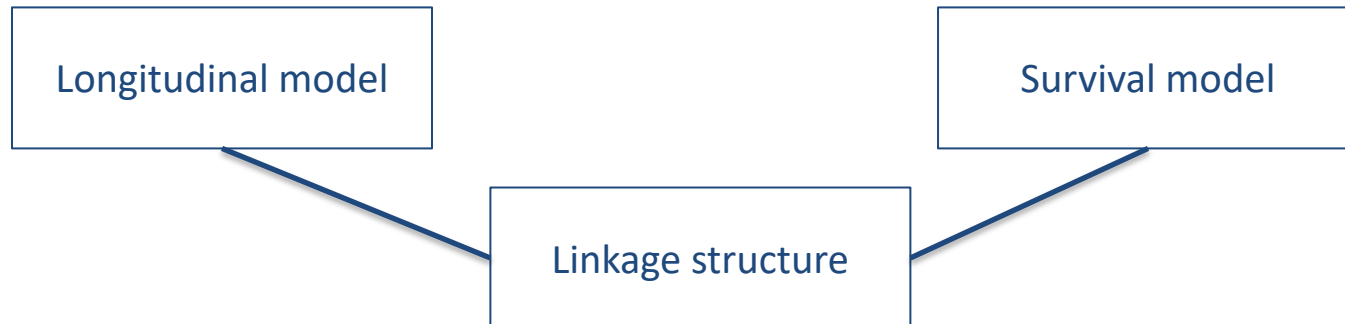
[Visser, 2007], [Atassi, 2014], [Rong, 2015], [Küffner, 2015], [Sun 2020], [Welsh 2022], [Rooney, 2016], [Pape,2020], [Ortholand, 2023]

« *Effect should be demonstrated on **mortality** and **function in daily activities** for example using ALSFRS_r.* » Treatment evaluation in ALS
[FDA, 2019]

Longitudinal and survival processes can be clinically linked which could reduce bias of the models [Lu, 2023].

[Eijk, 2019], [Wang, 2019], [Kyheng, 2021]

Joint models



	Joint latent class models [Proust-Lima, 2014]	Joint shared random effects models [Rizopoulos, 2011]
<i>Survival model</i>	Cox model with Weibull, piecewise constant or M-splines hazard	Cox model with splines hazard
<i>Longitudinal model</i>	GLM	GLM
<i>Linkage structure</i>	Compute class of patients that share common parameters for the two processes	Use the individual longitudinal trajectory as a covariate for the survival model
<i>Limitations</i>	Only have a probability of a patient belonging to a class	usually focus on how longitudinal outcomes impact survival

They depend on a reference time

Can we create a joint model that does not need a reference time?

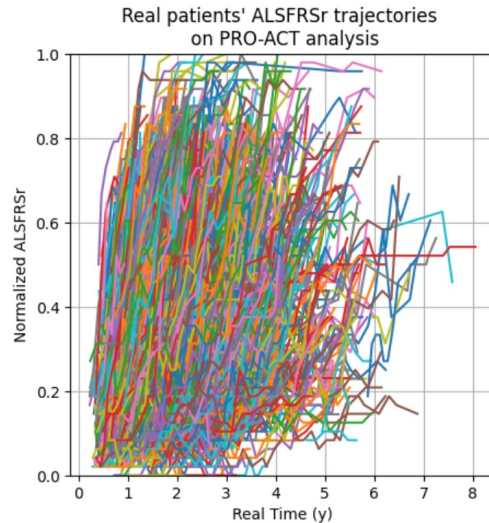
1. Method
1. Simulated data experiments
2. Application to ALS
3. Discussion

1. Method
 1. Model
 2. Benchmark
1. Simulated data experiments
2. Application to ALS
3. Discussion

We can consider N patients indexed by i

Longitudinal outcome

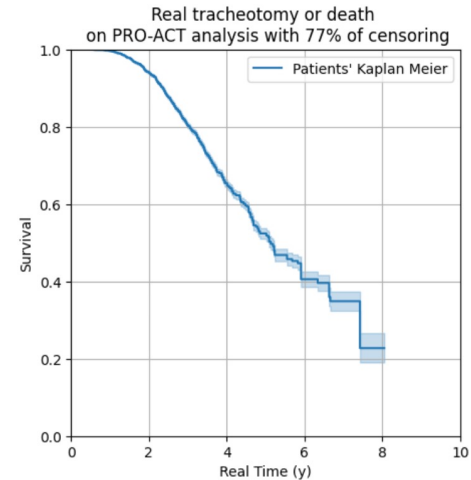
Outcome: $(t_{i,j}, y_{i,j})$



Survival outcome

X Observed event: (t_{ei} = time of event, True)

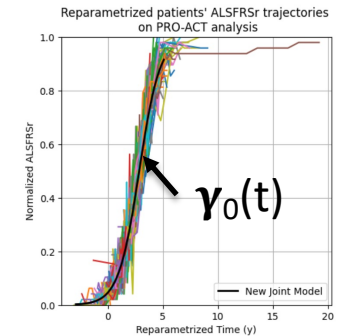
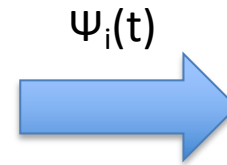
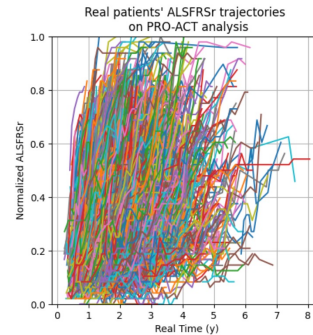
X Right censored event: (t_{ei} = time of censoring, False)



Main concept

Two types of parameters, to describe different concepts:

- **Random Effects (RE):** one patient
- **Fixed Effects (FE):** one population.



Two main phases

Fit:

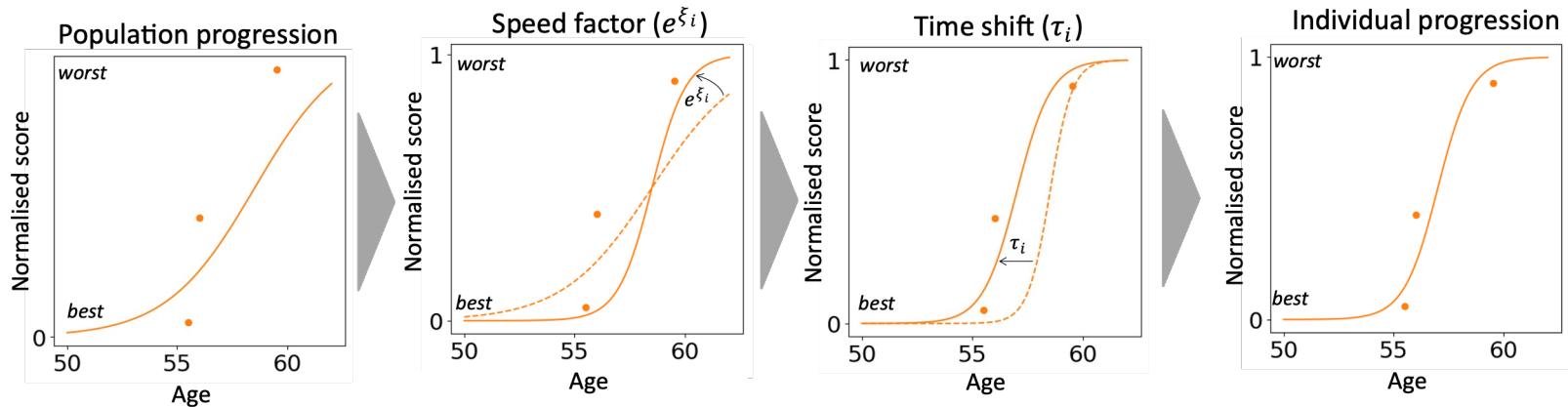
estimate random & fixed effects

Personalisation:

Knowing fixed effects estimate random effects

A bayesian mixed effect model based on Riemannian geometry

[Schiratti, 2015][Schiratti, 2017]



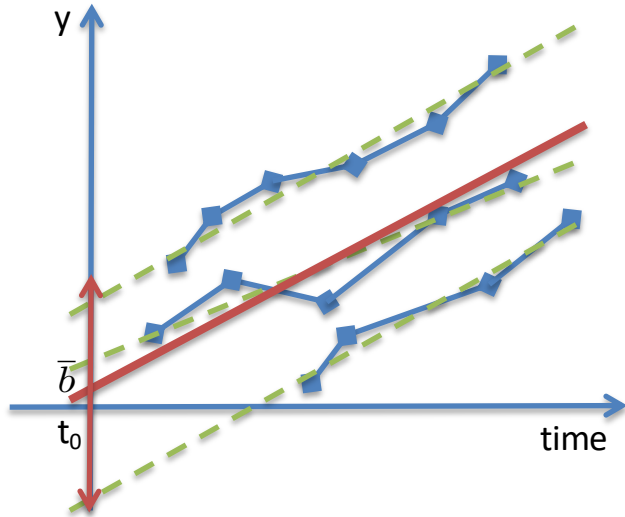
From ALS course map to individual trajectory : individual parameters adaptated from [Koval, 2021]

Latent disease age

$$\psi_i(t) = e^{\xi_i}(t - \tau_i) + t_0$$

Longitudinal model from latent disease age

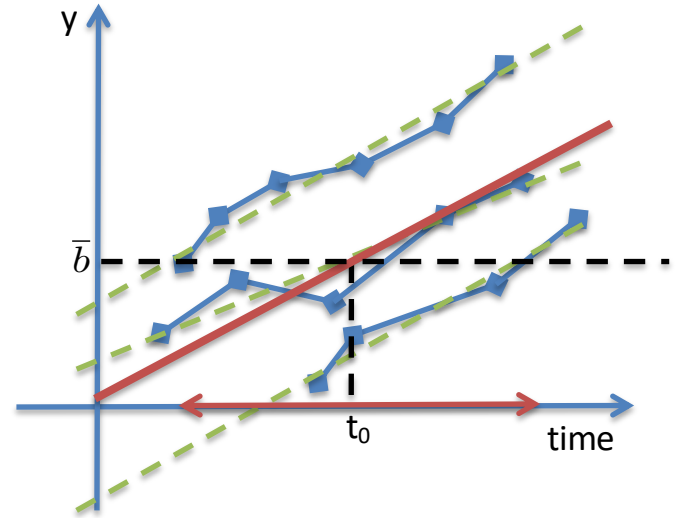
$$\gamma_0(\psi_i(t)) = (1 + g * \exp(-v_0(\psi_i(t) - t_0)))^{-1}$$



$$y_{ij} = (\bar{a} + a_i)(t_{i,j} - t_0) + \underbrace{\bar{b} + b_i}_{\text{Measurement of the } i^{\text{th}} \text{ subject at time } t_0} + \varepsilon_{i,j}$$

Measurement of the i^{th} subject at time t_0

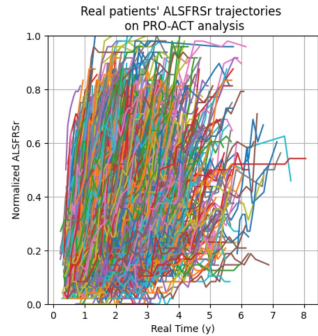
[Laird & Ware, 1982]



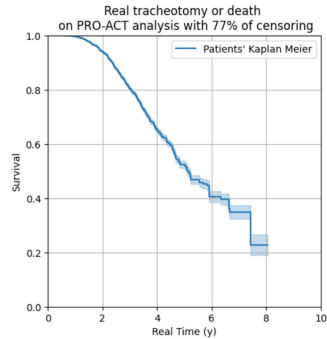
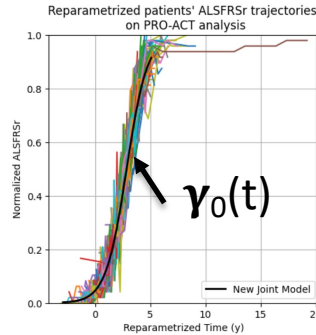
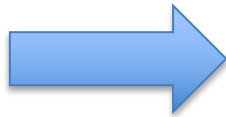
$$y_{ij} = \bar{a}a_i(t_{i,j} - \underbrace{t_0 - \tau_i}_{\text{Time at which measurement of the } i^{\text{th}} \text{ subject reaches } b}} + \bar{b} + \varepsilon_{i,j}$$

Time at which measurement of the i^{th} subject reaches b

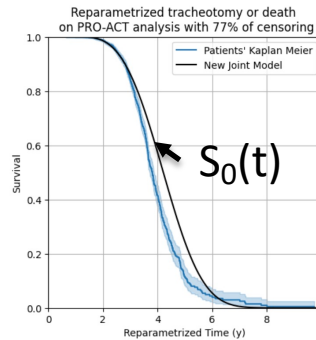
[Schiratti et al., 2015]



Latent disease age



$$\psi_i(t) = e^{\xi_i(t - \tau_i)} + t_0$$



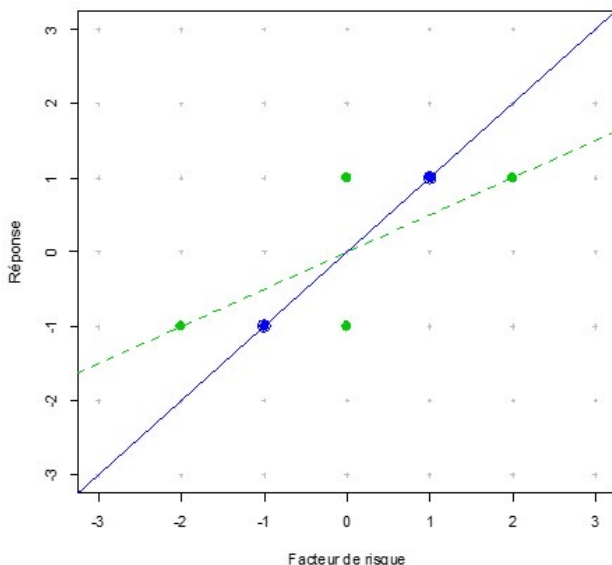
Logistic function

$$\gamma_0(\psi_i(t_{i,j})) = \left(1 + g * \exp(-v_0(\psi_i(t_{i,j}) - t_0))\right)^{-1}$$

Weibull distribution

$$S_0(\psi_i(t_{e_i})) = \exp\left(-\left(\frac{\psi_i(t_{e_i}) - t_0}{v}\right)^\rho\right)$$

Uncertainty on input data leads to bias on regression factor [Draper, 1998]



$$Y = a\hat{X} + b \text{ with } \hat{X} = X + \epsilon$$

$$\Rightarrow |a| \text{ underestimated}$$

In our model we don't know exactly the latent disease age ...

$$\widehat{\psi}_i(t) = \psi_i(t) + \epsilon$$

which might lead to biases...

$$\gamma_0(\widehat{\psi}_i(t)) = \left(1 + g * \exp\left(-v_0(\widehat{\psi}_i(t) - t_0)\right)\right)^{-1}$$

$$S_0(\widehat{\psi}_i(t)) = \exp\left(-\left(\frac{\widehat{\psi}_i(t) - t_0}{v}\right)^\rho\right)$$

We corrected our estimated values using RE means computed with personalization from training set

1. Method

1. Model

2. Benchmark

1. Simulated data experiments

2. Application to ALS

3. Discussion

We want to compare our model to different state of the art models

Longitudinal model

The existing Longitudinal model [leaspy]

Longitudinal

Basic survival model

AFT model
With Weibull fonction [lifeline]

AFT

Two steps survival model

Use the random effect of the Longitudinal model
As covariates in the AFT model
With Weibull fonction [lifeline]

Two-step

SOTA Joint model

Shared random effects models
Logistic RM but spline survival [JMbayes2]

JMbayes2

We now need metrics to compare them

Mean Absolute Error

best: 0, worst: +inf

Measure the distance between the truth and the prediction

Hand computation

Uno's Concordance Index

best: 1, worst: 0.5

Proportion of all comparable pairs that were ordered correctly by the model taking into account censoring.

`concordance_index_censored` from `sksurv` package

Integrated Brier score (IBS)

best: 0, worst: +inf

The Brier score is an extension of the mean squared error to right censored data. The IBS provides an overall calculation of the model performance at all available times.

`integrated_brier_score` from `sksurv` package

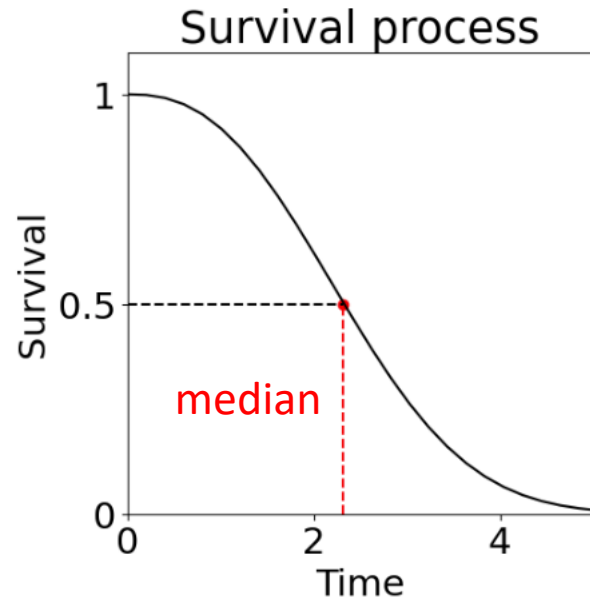
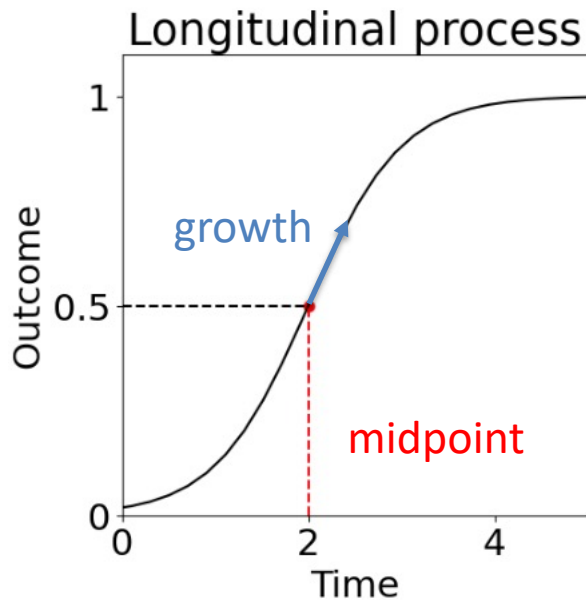
Cumulative dynamic AUC

best: 1, worst: 0

It quantifies how well a model can distinguish subjects who fail by a given time from subjects who fail after this time, for several times. It is also corrected for censoring.

`cumulative_dynamic_auc` from `sksurv` package

Parameters value can be hard to interpret, thus we choose to use clinically meaningful parameters

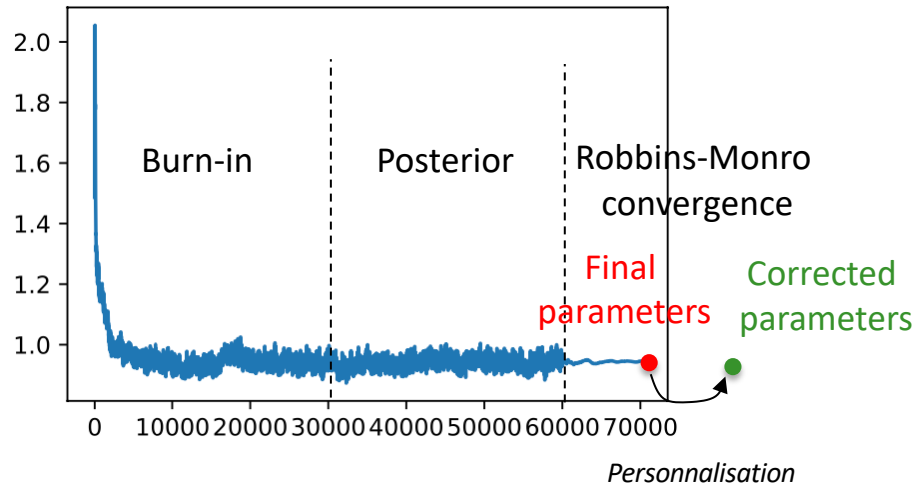


1. Model method
1. Simulation study
 1. Method
 2. Results
2. Application to ALS
3. Discussion

We have simulated data using the Longitudinal model and a Weibull distribution using parameters extracted from a real ALS dataset

We tested different study designs to make a sensitivity analysis [Hickey, 2016]

	Easy	Medium	Hard
Patient number (patients)	1,000	500	200
Visit density (months)	1	1.47	3
Follow-up (years)	2	0.96	0.5
Longitudinal noise (pt ALSFRSr)	4	10	20
Survival standard deviation (years)	2.44	2.74	3.37

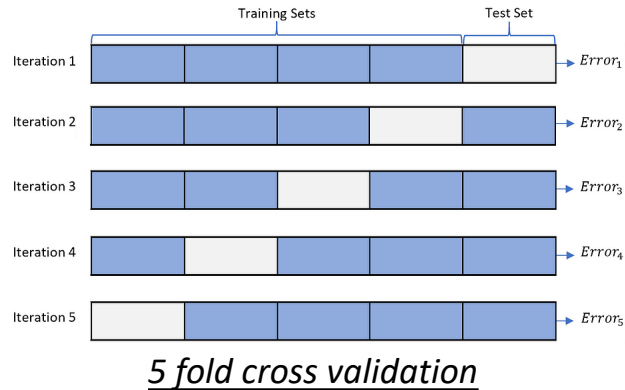


Parameters estimation

- Bias on fix effects,
- Intra-class correlation of RE using final parameters.

Dilution bias correction

- Clinically meaningful parameters.



Data

- Real-like simulated data
- Patients with at least 3 visits

Experiment set-up

- 10 folds cross-validation
- Two visits to predict the remaining visits

Model comparison

Clinically Meaningful Parameters (CMP):

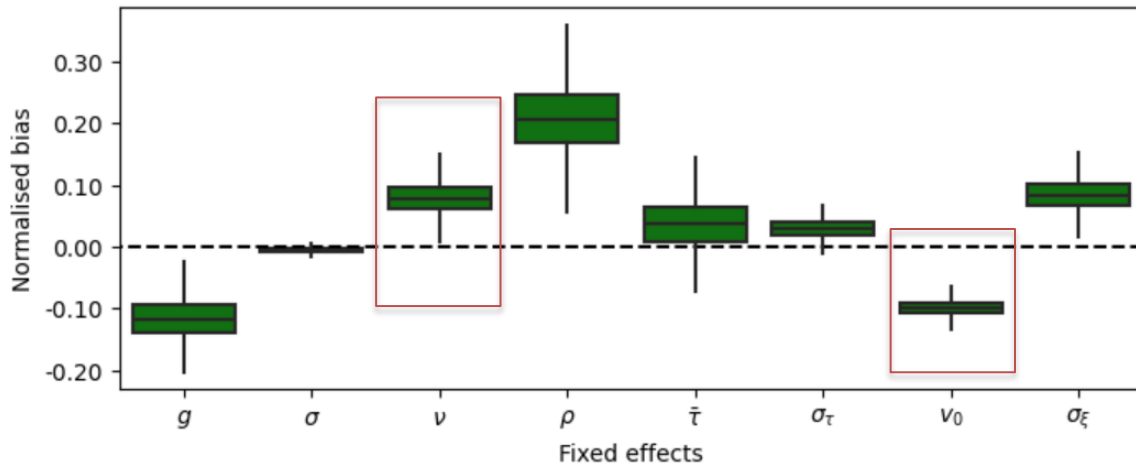
- Bias from simulated ones

Predictions:

- Survival: AUC, C-Index, IBS,
- Longitudinal: absolute error.

1. Model method
1. Simulation study
 1. Method
 2. Results
2. Application to ALS
3. Discussion

We can check MCMC posterior parameters estimation
[Gelman and Rubin, 1992]



We have checked all simulated data sets and the parameters bias goes from -0.25 to 0.50.

Intra-class correlation:

ξ : 0.88 (CI95% = [0.86, 0.89])

τ : 0.95 (CI95% = [0.94, 0.95])

We have checked all simulated data sets and the parameters bias goes from 0.69 to 0.96.

What is really important is clinically meaningful parameters which could be corrected

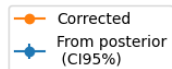
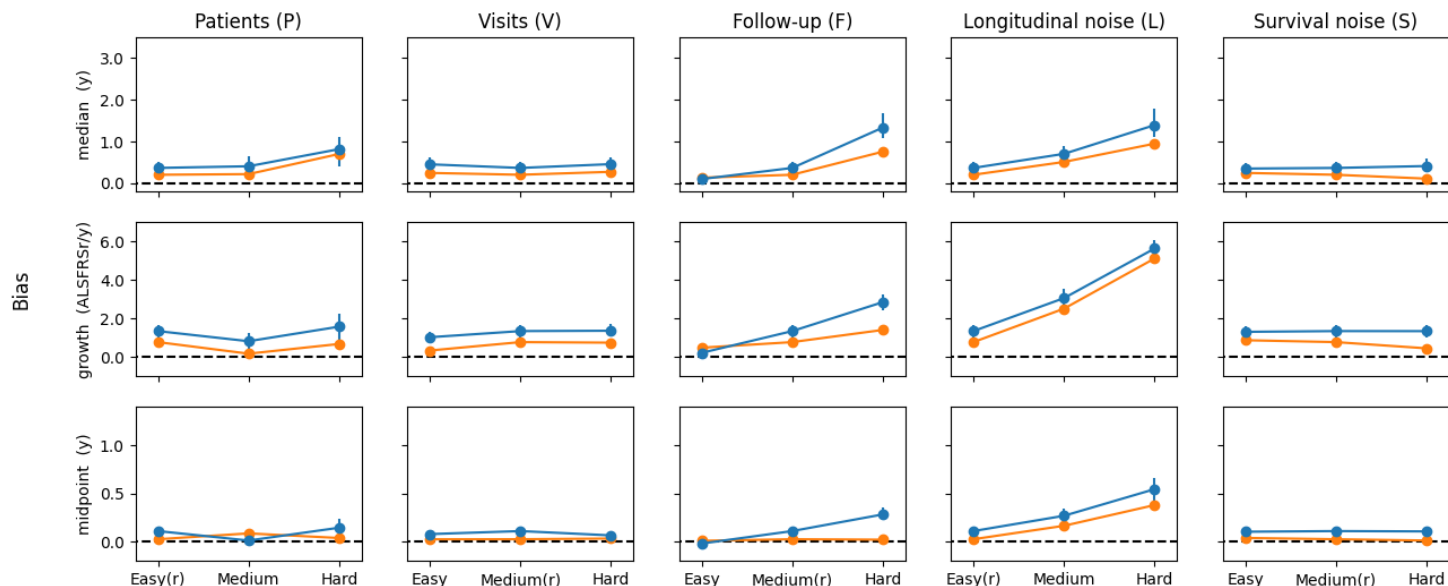
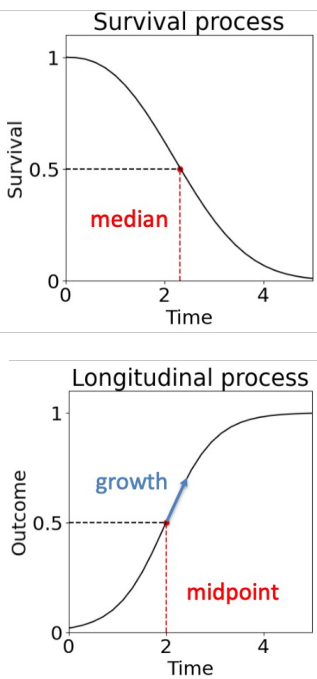


Figure 1 Absolute estimated bias for clinically meaningful estimated parameters (median, growth and midpoint) for all simulated data

Legend: corrected bias: mean extracted from Robbin Monroe algorithm after attenuation bias correction, from posterior: mean with CI 95% of the posterior MCMC chain. Datasets with (r) correspond to the real-like dataset. Values of the clinically meaningful estimated parameters that enabled the simulation, from which the bias is computed, are 4.36 ± 0.12 years for the median, -13.13 ± 0.21 ALSFRSr point per year for the growth, 2.92 ± 0.06 years for the midpoint.

	Joint	Two stages	p-value	Longitudinal	p-value	AFT	p-value	JMbayes2	p-value
growth	0.514 (0.083)	-	-	0.379 (0.078)	2.0e-02	-	-	1.597 (0.111)	3.9e-03
midpoint	0.008 (0.006)	-	-	0.045 (0.009)	3.9e-03	-	-	0.402 (0.04)	3.9e-03
median	0.34 (0.068)	0.11 (0.029)	5.9e-03	-	-	0.833 (0.062)	5.9e-03	2.234 (0.111)	5.9e-03

Clinically Meaningfull Parameters bias

	Joint	Two stages	p-value	Longitudinal	p-value	AFT	p-value	JMbayes2	p-value
Absolute bias ↓	3.759 (3.868)	-	-	3.716 (3.795)	1.7e-02	-	-	10.347 (8.466)	0.0e+00
IBS ↓	0.091 (0.021)	0.08 (0.018)	2.9e-03	-	-	0.113 (0.029)	6.7e-04	0.114 (0.03)	7.6e-04
Mean AUC (1y, 1.5y) ↑	0.752 (0.079)	0.767 (0.084)	1.0e+00	-	-	0.602 (0.115)	6.1e-03	0.6 (0.118)	6.0e-03
C-index 1.0y ↑	0.754 (0.059)	0.769 (0.063)	9.3e-01	-	-	0.615 (0.091)	4.6e-03	0.612 (0.092)	4.0e-03
C-index 1.5y ↑	0.749 (0.058)	0.766 (0.057)	3.3e-01	-	-	0.615 (0.09)	4.6e-03	0.611 (0.093)	3.8e-03

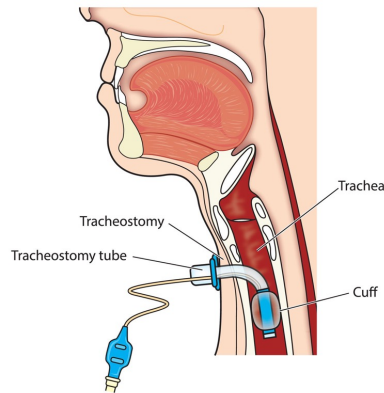
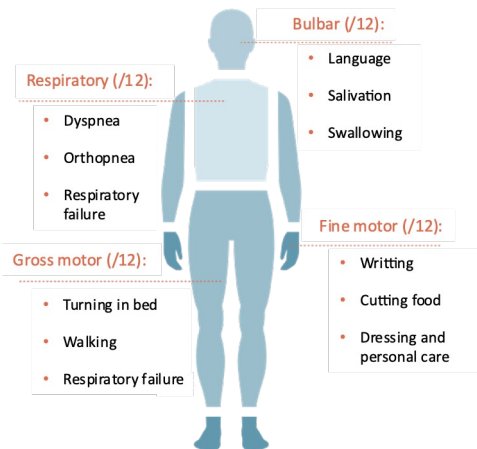
Prediction metrics

1. Model method
1. Simulation study
2. Application to ALS
 1. Method
 2. Results
3. Discussion

PRO-ACT database: aggregation of 23 phase II and III clinical trials and one observational study

Patient algorithm:

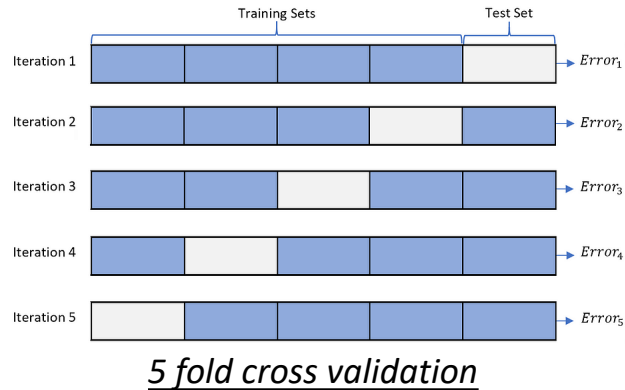
- 3 visits for ALSFRS_r,
- age at first symptoms,
- symptom onset (spinal or bulbar),
- sex.



Data processing:

- normalisation using a score scale
- First symptoms as reference time
- event: tracheotomy or death

Characteristics	Values
Number of patients	2,529
Number of visits	23,162
Number of patients years	2,535
Percentage of censored events (%)	76.7
Number of visits per pat	9.2 ± 4.3
Time of follow-up (y)	1.0 ± 0.6
Time between visits (m)	1.5 ± 0.9
Gender (Male)	1575 (62.3 %)
Symptom onset (Spinal)	1953 (77.2 %)
Age at first symptoms	54.0 ± 11.3
Time from first symptoms to baseline (y)	1.6 ± 0.9
ALSFRS _r total (at baseline)	37.9 ± 5.4



Data

- PROACT data
- Patients with at least 3 visits

Experiment set-up

- 10 folds cross-validation
- Two visits to predict the remaining visits

Model comparison

Clinically Meaningful Parameters (CMP):

- Variation from one model to the other

Predictions:

- Survival: AUC, C-Index, IBS,
- Longitudinal: absolute error.

1. Model method
1. Simulation study
- 2. Application to ALS**
 1. Method
 - 2. Results**
3. Discussion

	Joint	Two stages	p-value	Longitudinal	p-value	AFT	p-value	JMbayes2	p-value
growth	-13.219 (0.084)	-	-	-13.98 (0.079)	1.3e-11	-	-	-15.351 (0.118)	5.3e-13
midpoint	2.831 (0.011)	-	-	2.786 (0.011)	8.2e-10	-	-	3.222 (0.014)	4.9e-13
median	4.155 (0.035)	4.071 (0.015)	1.1e-04	-	-	4.666 (0.024)	2.2e-10	4.392 (0.118)	2.4e-04




Clinically Meaningfull Parameters

	Joint	Two stages	p-value	Longitudinal	p-value	AFT	p-value	JMbayes2	p-value
Absolute bias ↓	4.083 (4.244)	-	-	4.192 (4.396)	2.2e-48	-	-	5.42 (5.687)	1.5e-212
IBS ↓	0.103 (0.014)	0.106 (0.011)	2.1e-01	-	-	0.127 (0.009)	1.1e-04	0.093 (0.012)	3.3e-04
Mean AUC (1y, 1.5y, 2y) ↑	0.672 (0.072)	0.619 (0.086)	1.3e-02	-	-	0.412 (0.07)	5.5e-05	0.624 (0.094)	2.9e-03
C-index 1.0y ↑	0.699 (0.046)	0.635 (0.06)	5.8e-04	-	-	0.408 (0.05)	7.8e-07	0.64 (0.059)	4.4e-04
C-index 1.5y ↑	0.705 (0.046)	0.657 (0.055)	1.4e-03	-	-	0.408 (0.05)	1.1e-06	0.668 (0.049)	4.8e-04
C-index 2.0y ↑	0.706 (0.048)	0.672 (0.052)	3.8e-03	-	-	0.408 (0.05)	1.9e-06	0.679 (0.048)	3.6e-04




Prediction metrics

1. Model method
1. Simulation study
2. Application to ALS
3. Discussion

Strength

-  Prediction error (MAE: 4.083) not far from Minimum Detectable Change (1.59)
-  Interpretable parameters
-  Tested on many scenarios enable to give guidelines

Limits

-  Independence of longitudinal noises at each visit assumption
-  Improve dilution bias correction
-  More flexible hazard function

Soon available in

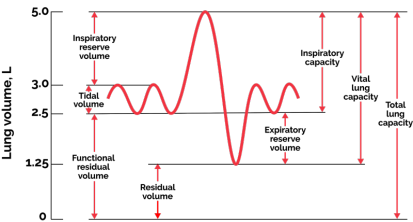


Discussion

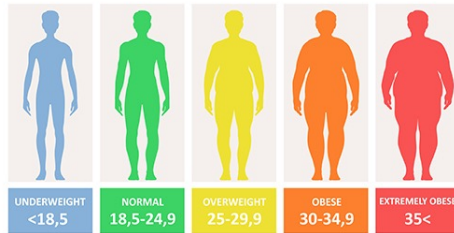
Conclusion & perspectives

Our joint model with latent disease age is better suited than state-of-the-art joint models when the reference time is not well defined.

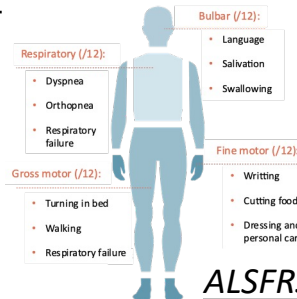
Many longitudinal outcomes



Vital Capacity

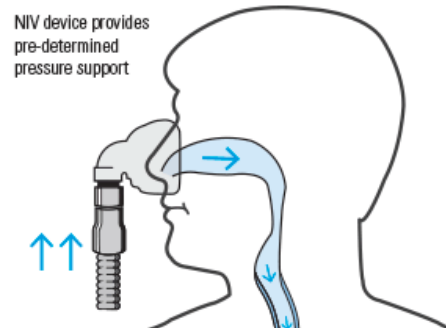


BMI

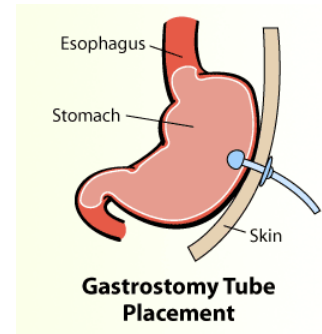


ALSFRSr score

Many events



Non Invasive Ventilation



Gastrostomy Tube Placement

Gastrostomy

Thank you for your attention

And many thanks to the member of my team and the ARAMIS lab

Happy to take questions!