Longitudinal and survival joint prediction: time reparameterization in amyotrophic lateral sclerosis context

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Longitudinal and survival joint modelling prediction: time reparametrization in Amyotrophic Lateral Sclerosis context

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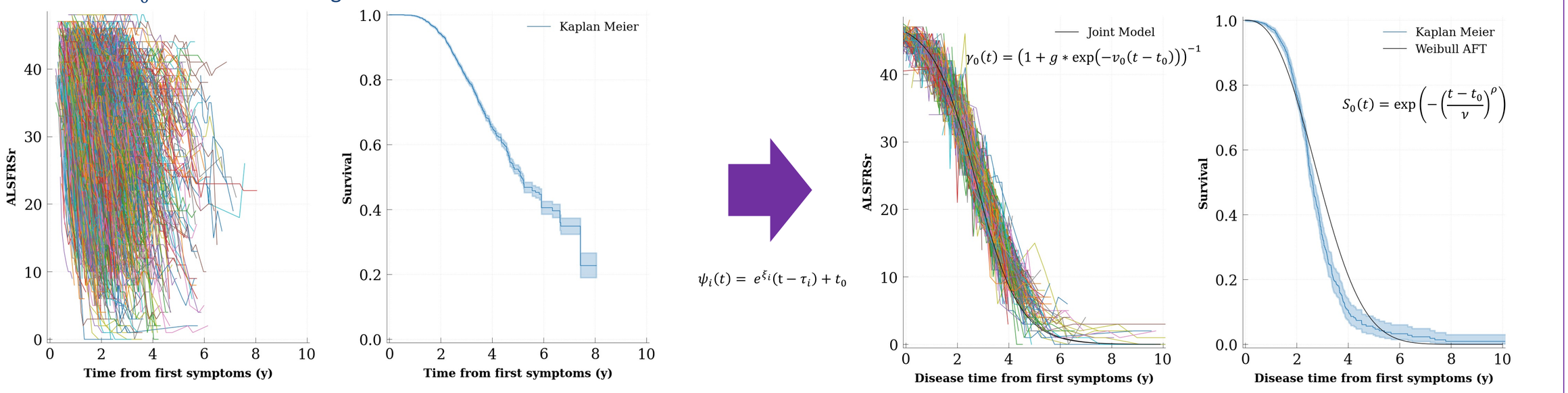
Background & Objectives

Neurodegenerative diseases, among which Amyotrophic Lateral Sclerosis, have no precise starting time. Nevertheless, in Joint modelling, most models use Generalised Linear Mixed-effects Models (GLMM) to model the longitudinal process. Such kind of model, by design, needs a reference time. An existing longitudinal model does not need that reference time but has never been extended to a Joint model. It has also the advantage to create a latent disease age (Schiratti et al., 2015).

We validated and bench-marked a new Joint model with latent disease age that does not need a reference time.

Methods

We created a non-linear joint model with shared random effects composed of a time reparametrization into the disease age ψ_i for each patient, a longitudinal model γ_0 and a survival model S_0 from the disease age .



We evaluated it against, two one-process-only models, an AFT model using Lifelines package (Davidson-Pilon, 2019) and the existing longitudinal model using Leaspy package, a two-stage model using AFT and the existing longitudinal model and a joint model with shared random effects using JMbayes2 package.

Simulation Results

Data We have simulated data thanks to real-like parameters extracted from PRO-ACT ALS data, using the existing longitudinal model and AFT model. We have simulated 1,000 patients with an average of 8 visits for a follow-up of 1 year with 85 % censored events and a noise of 5% on the longitudinal process.

Cohort description We compared the progression of the patients with mean random effects.

	Joint	Two stages	p-value	Longitudinal	p-value	AFT	p-value	JMbayes2	p-value
growth	**0.318 (0.13)**	-	-	0.409 (0.089)	4.6e-01	-	-	2.03 (0.116)	3.9e-03
midpoint	**0.035 (0.018)**	-	-	0.102 (0.011)	3.9e-03	-	-	0.058 (0.031)	2.6e-01
median	0.255 (0.065)	**0.231 (0.051)**	1.0e+00	-	-	0.698 (0.089)	5.9e-03	3.192 (0.241)	5.9e-03

Table 1 Absolute clinically meaningful estimated parameters bias on real-like dataset

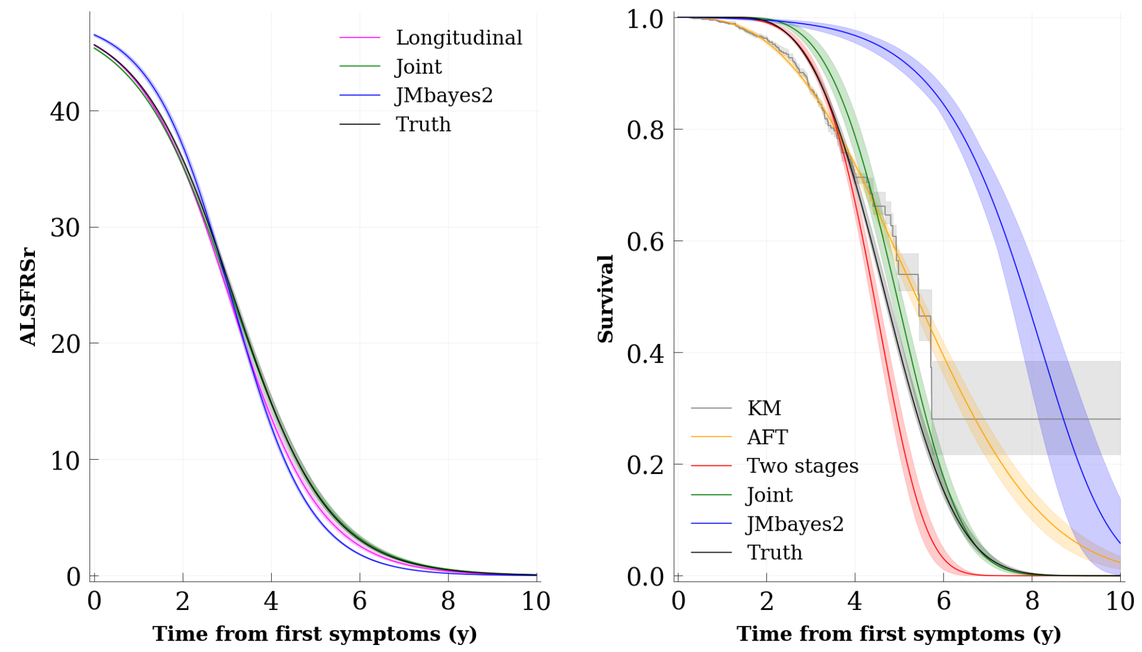


Figure 1 Average patient curve on real-like dataset

Prediction We have made a 10-fold cross-validation using two visits to predict the longitudinal outcome at the remaining visits and the event.

	Joint	Two stages	p-value	Longitudinal	p-value	AFT	p-value	JMbayes2	p-value
Absolute bias ↓	**3.561 (3.579)**	-	-	3.596 (3.682)	1.3e-01	-	-	3.981 (3.892)	3.6e-33
IBS ↓	0.155 (0.033)	**0.147 (0.033)**	4.3e-02	-	-	0.196 (0.039)	1.8e-03	0.198 (0.039)	3.7e-04
C-index 1.0y ↑	0.654 (0.04)	**0.658 (0.038)**	1.0e+00	-	-	0.531 (0.047)	1.3e-04	0.536 (0.05)	1.4e-04
C-index 1.5y ↑	0.656 (0.038)	**0.666 (0.037)**	5.2e-02	-	-	0.531 (0.047)	1.0e-04	0.537 (0.05)	1.2e-04
C-index 2.0y ↑	0.66 (0.034)	**0.668 (0.034)**	2.5e-03	-	-	0.531 (0.047)	6.1e-05	0.539 (0.051)	9.9e-05

Table 2 Prediction metrics on real-like dataset

Real Data Results

Data We used PRO-ACT a large multi-centric ALS cohort. We had access to 2,529 patients with an average of 9.2 ± 4.3 for a follow-up of 1 ± 0.6 with 76.7 % of censored events. We have normalised the score using its natural scale on 48.

Cohort description We compared the progression of the patients with mean random effects.

	Joint	Two stages	p-value	Longitudinal	p-value	AFT	p-value	JMbayes2	p-value
growth	-13.233 (0.094)	-	-	-13.98 (0.079)	2.0e-11	-	-	-15.351 (0.118)	3.6e-13
midpoint	2.841 (0.011)	-	-	2.786 (0.011)	2.0e-09	-	-	3.222 (0.014)	6.8e-13
median	4.185 (0.038)	4.071 (0.015)	2.4e-05	-	-	4.666 (0.024)	6.1e-10	4.392 (0.118)	7.5e-04

Table 3 Clinically meaningful estimated parameters bias on real-like dataset

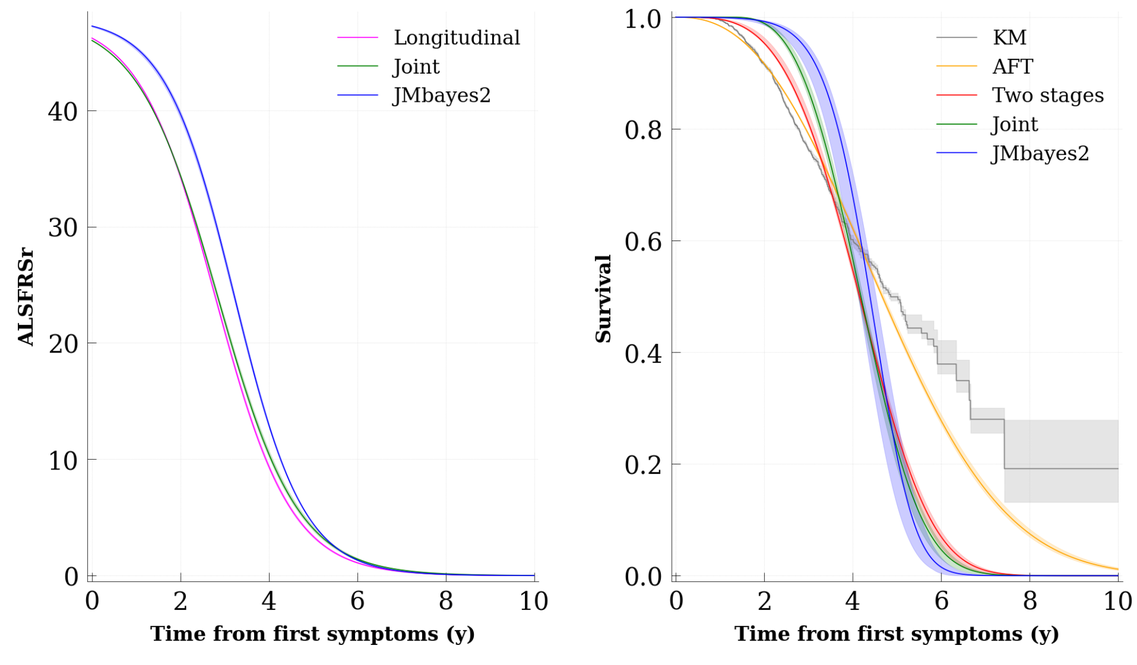


Figure 2 Average patient curve on PRO-ACT dataset

Prediction We have made a 10-fold cross-validation using two visits to predict the longitudinal outcome at the remaining visits and the event.

	Joint	Two stages	p-value	Longitudinal	p-value	AFT	p-value	JMbayes2	p-value
Absolute bias ↓	**4.1 (4.264)**	-	-	4.192 (4.396)	1.2e-20	-	-	5.42 (5.687)	6.5e-201
IBS ↓	0.245 (0.04)	0.238 (0.036)	2.6e-01	-	-	0.267 (0.027)	1.0e-01	**0.222 (0.032)**	2.1e-03
C-index 1.0y ↑	**0.693 (0.047)**	0.612 (0.065)	2.9e-04	-	-	0.408 (0.05)	6.5e-07	0.64 (0.059)	3.3e-04
C-index 1.5y ↑	**0.7 (0.046)**	0.644 (0.058)	1.3e-03	-	-	0.408 (0.05)	9.0e-07	0.668 (0.049)	4.8e-04
C-index 2.0y ↑	**0.704 (0.046)**	0.664 (0.053)	4.0e-03	-	-	0.408 (0.05)	1.4e-06	0.679 (0.048)	1.4e-03

Table 4 Prediction metrics on real-like dataset

Conclusion

As it does not need reference time our joint model with latent disease age enables us to improve the performance of most of the prediction metrics compare to existing joint models. To continue developing this model, future improvement could consider adding more flexibility to the survival function and integrating the use of covariates or modelling of several longitudinal outcomes or events.

https://gitlab.com/icm-institute/aramislab/leaspy

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