Bayesian Analysis of Amyotrophic Lateral Scleroris Functional Score

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ALS Progression

Table 2: The ALSFRS-R – a functional amyotrophic lateral sclerosis rating scale incorporating assessments of respiratory function[28]

Item	Scoring criteria	
1. Speech	4	Normal speech process
	3	Detectable speech disturbance
	2	Intelligible with repeating
	1	Speech combined with non-vocal communication
	0	Loss of useful speech
2. Salivation	4	Normal
	3	Slight but definite excess of saliva in mouth; may have nighttime drooling
	2	Moderately excessive saliva; may have minimal drooling (during the day)
	1	Marked excess of saliva with some drooling
	0	Marked drooling; requires constant tissue or handkerchief
3. Swallowing	4	Normal eating habits
	3	Early eating problems – occasional choking
	2	Dietary consistency changes
	1	Needs supplement tube feeding
	0	NPO (exclusively parenteral or enteral feeding)
4. Handwriting	4	Normal
	3	Slow or sloppy, all words are legible
	2	Not all words are legible
	1	Able to grip pen, but unable to write
	0	Unable to grip pen
5a. Cutting food and handling utensils*	4	Normal
	3	Somewhat slow and clumsy, but no help needed
	2	Can cut most foods (>50%), although slow and clumsy; some help needed
	1	Food must be cut by someone, but can still feed slowly
	0	Needs to be fed
5b. Cutting food and handling utensils	4	Normal
	3	Clumsy, but able to perform all manipulation independently
	2	Some help needed with closures and fasteners
	1	Provides minimal assistance to caregiver
	0	Unable to perform any aspect of task
6. Dressing and hygiene	4	Normal function
	3	Independent and complete self-care with effort or decreased efficiency
	2	Intermittent assistance or substitute methods
	1	Needs attendant for self-care
	0	Total dependence
7. Turning in bed and adjusting bed clothes	4	Normal function
	3	Somewhat slow and clumsy but no help needed
	2	Can turn alone, or adjust sheets, but with great difficulty
	1	Can initiate, but not turn or adjust sheets alone
	0	Helpless
8. Walking	4	Normal
	3	Early ambulation difficulties
	2	Walks with assistance
	1	Non-ambulatory functional movement
	0	No purposeful leg movement
9. Climbing stairs	4	Normal
	3	Slow
	2	Mild unsteadiness or fatigue
	1	Needs assistance
	0	Cannot do
10. Dyspnea	4	None
	3	Occurs when walking
	2	Occurs with one or more of the following: eating, bathing, dressing
	1	Occurs at rest: difficulty breathing when either sitting or lying
	0	Significant difficulty: considering using mechanical respiratory support
11. Orthopnea	4	None
	3	Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows
	2	Needs extra pillows in order to sleep (more than two)
	1	Can only sleep sitting up
	0	Unable to sleep without mechanical assistance
12. Respiratory insufficiency	4	None
	3	Intermittent use of BiPAP
	2	Continuous use of BiPAP during the night
	1	Continuous use of BiPAP during the day and night
	0	Invasive mechanical ventilation by intubation or tracheotomy

*Patients without G-tube – use 5b if >50% is though G-tube.
**Patients with G-tube – 5b is used if the patient has a G-tube and only if it is the primary method (>50%) of eating.
ADL = activities of daily living; BiPAP = Bilevel Positive Airway Pressure;
G-tube = gastrostomy tube; NPO = nothing by mouth.
Reproduced with permission from Cedarbaum et al., 1999.[28]

To evaluate the progression of the disease we can use **ALSFRS-R**.

AIM: Find a good model to predict the evolution of the disease

Data Preprocessing

- Compute ALSFRS-R (Revised score)
- Joining datasets
  - left_join with ALSFRS on the LHS
  - join with interpolation of longitudinal covariates
- Missing values problem:
  - Threshold for NA in a variable: 35%
  - Fill fixed variables with median
  - Fill longitudinal variables with MICE package

Mixed Effect Model

$j = 1, \dots, m$ patient, $i = 1, \dots, n_j$ temporal observations for patient j

Mixed Effect Model

$$Y_{ij} = \underline{X}_{ij}^T \underline{\theta} + \underline{Z}_{ij}^T \underline{\gamma}_j + \epsilon_{ij},$$

$$\epsilon_{ij} \,|\, \sigma^2 \overset{iid}{\sim} \mathcal{N}(0, \sigma^2)$$

where $\underline{\theta} \in \mathbb{R}^P$ is fixed coeff. and $\underline{\gamma}_j \in \mathbb{R}^K$ random coeff. for $patient_j$

Priors:

$$\begin{aligned} \gamma_{jk} \,|\, \tau_k^2 &\overset{iid}{\sim} \mathcal{N}(0, \tau_k^2) \\ \theta_p &\overset{iid}{\sim} \mathcal{N}(0, \gamma_0^2) \\ \tau_k^2 &\overset{iid}{\sim} inv - gamma(a_1, b_1) \\ \sigma^2 &\sim inv - gamma(a_2, b_2) \end{aligned} \qquad \begin{aligned} &\forall j = 1, \dots, m, \\ &\forall k = 1, \dots, K, \\ &\forall p = 1, \dots, P \end{aligned}$$

Model: summary of the previous Steps

ALSFRS vs Delta

$$\mathbb{E}\left[ALSFRS_{ij}\right] = \theta_0 + \theta_1 t_{ij} + \gamma_{0j} + \gamma_{1j} t_{ij}$$

$$D = \mathcal{I}_{Bulbar} = \begin{cases} 1, & if \;\; Als - type = Bulbar \\ 0, & otherwise \end{cases}$$

ALSFRS vs Delta & Onset

$$\mathbb{E}\left[ALSFRS_{ij}\right] = \theta_0 + \theta_1 t_{ij} + \theta_2 D_j + \theta_3 t_{ij} D_j + \gamma_{0j} + \gamma_{1j} t_{ij}$$

Medication

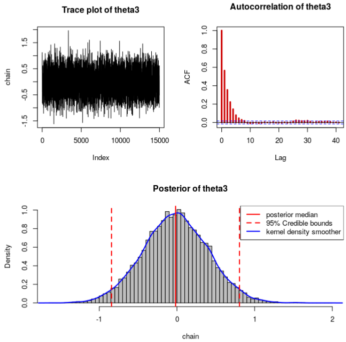
Two different medication, an indicator for the RILUZOLE and an indicator that tells us if any individual patient received medication or a placebo.

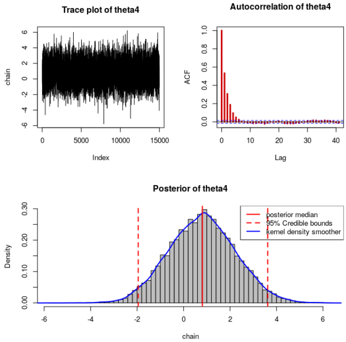
$$P = \mathcal{I}_{Placebo} = \begin{cases} 1, & if \;\; Treatment - type = Placebo \\ 0, & if \;\; Treatment - type = Active \end{cases}$$

$$R = \mathcal{I}_{RILUZOLE} = \begin{cases} 1, & if \;\; the \;\; patient \;\; assumed \;\; RILUZOLE \\ 0, & if \;\; otherwise \end{cases}$$

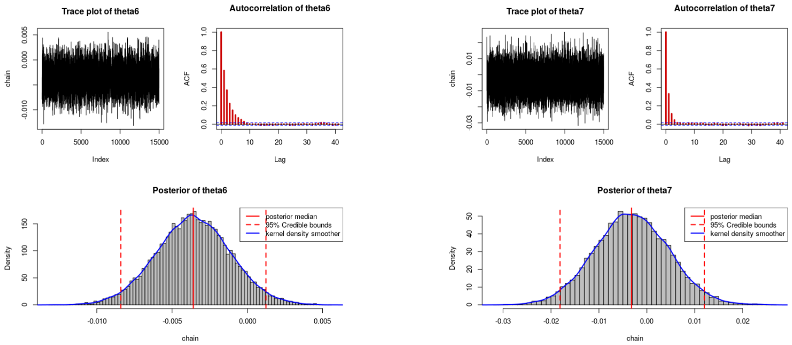
Medication

$$
\begin{aligned}
\mathbb{E}\left[ALSFRS_{ij}\right] &= \theta_0 + \theta_1 t_{ij} + \theta_2 D_j + \theta_3 P_j + \theta_4 R_j \\
&+ \theta_5 t_{ij} D_j + \theta_6 t_{ij} P_j + \theta_7 t_{ij} R_j + \gamma_{0j} + \gamma_{1j} t_{ij}
\end{aligned}
$$





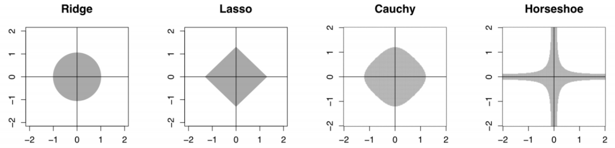
Medication



It doesn't seem to be strong statistical evidence in keeping these variables, but we will investigate more deeply this aspect later.

Horseshoe Prior

Sparsity problem due to the number of degrees of freedom of our model (23 covariates) $\rightarrow$ Horseshoe prior for variable selection

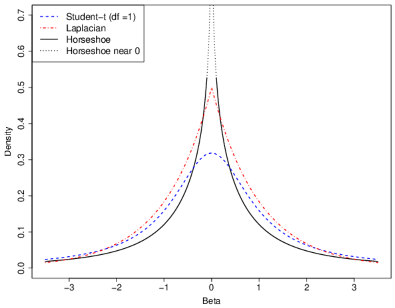


If we want to understand how this regularization works, we can see the comparison of the unit ball from classical regularization (Ridge, Lassu, Cauchy) and the Horseshoe.

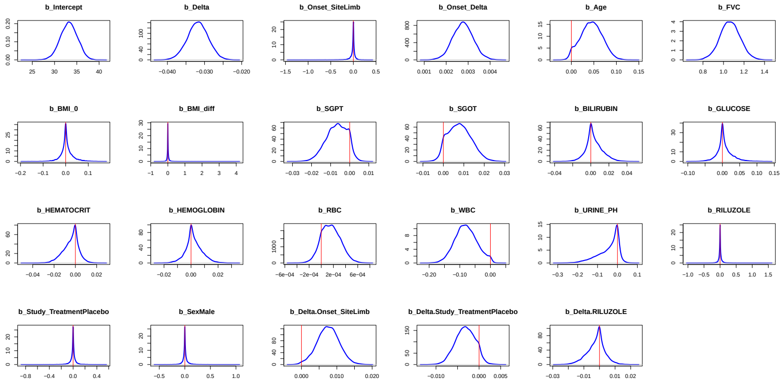
Horseshoe Prior

New priors for thetas:

$$\theta_p \,|\, \tau,\, \lambda_p \overset{iid}{\sim} \mathcal{N}(0, \tau\lambda_p)$$
$$\lambda_p \overset{iid}{\sim} C^+(0,1)$$
$$\tau \sim C^+(0, \tau_0)$$
$$\forall p = 1, \ldots, P$$



Variable selection



Cosine Basis Expansion

By looking at the partial autocorrelations of the functional rating scores for each patient one can clearly see a wavy dependence for this reason we implemented the following basis expansion:

$$f(t_{ij}) = \underline{\beta}_{0j} + \underline{\beta}_{1j} t_{ij} + \sum_{k=1}^{3} \underline{\beta}_{(k+1)j} \cos\left(\frac{k\pi(t_{ij} - t_{(1)j})}{t_{(n_j)j} - t_{(1)j}}\right)$$

where:

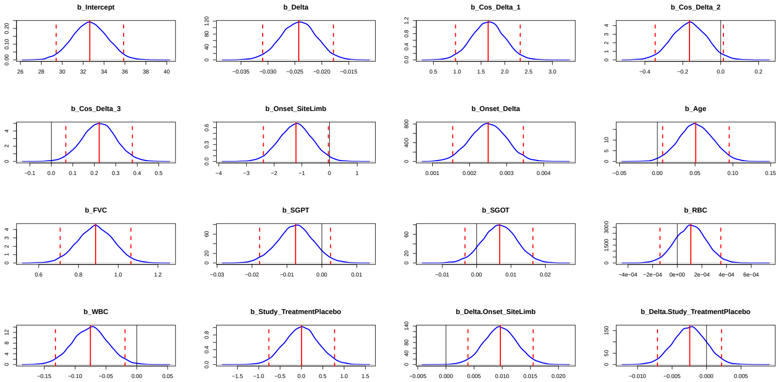
$$\underline{\beta}_{lj} = \underline{\theta}_{l} + \underline{\gamma}_{lj} \qquad \forall l = 0, \dots, 4$$

Final model

Final model

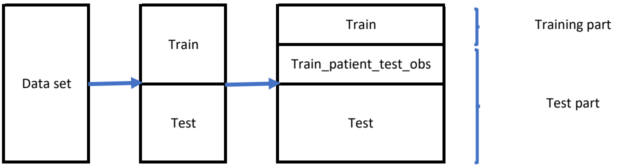
$$
\begin{aligned}
\mathbb{E}\left[ALSFRS_{ij}\right] = & \, f(t_{ij}) + \theta_5 D_j + \theta_6 Onset\_Delta_j + \theta_7 Age_j + \theta_8 FVC_{ij} \\
& + \theta_9 SGPT_{ij} + \theta_{10} SGOT_{ij} + \theta_{11} RBC_{ij} + \theta_{12} WBC_{ij} \\
& + \theta_{13} P_j + \theta_{14} Onset\_Delta_j \; t_{ij} + \theta_{15} P_j \; t_{ij}
\end{aligned}
$$

Posterior Credible Intervals



Data subdivision

First we divided our dataset in two parts: train and test and then we took the train data and for the first half of patients we put their second half of time observations in a new dataset that was named *train-patient-test-observation*.



Errors

The first error is a mean absolute error:

$$err_{1_{ij}} = \left| \mathbb{E}\left[Y_{ij}^{sim} \right] - Y_{ij}^{true} \right| \approx \left| \left(\frac{1}{M} \sum_{k=1}^{M} Y_{ij}^{(k)} \right) - Y_{ij}^{true} \right|$$

where we used the MCMC approximation and M is the number of iterations.

$$err_1 = \frac{1}{n} \sum_{j=1}^{m} \sum_{i=1}^{n_j} err_{1_{ij}} \quad \text{with} \quad n = \sum_{j=1}^{m} n_j$$

The second error takes in consideration the variability of the prediction:

$$err_{2_{ij}} = err_{1_{ij}} + |CI_{95\%}|_{ij}$$

$$err_2 = \frac{1}{n} \sum_{j=1}^{m} \sum_{i=1}^{n_j} err_{2_{ij}}$$

Errors

Model Onset site

	Training set	Train with new obs.	Test set
err_1	1.353407	3.808556	6.555238
err_2	10.62259	20.34279	40.21576

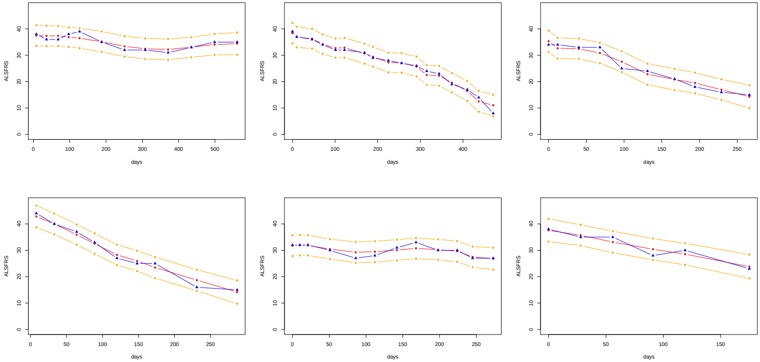
Model Medication

	Training set	Train with new obs.	Test set
err_1	1.353605	3.7856	6.587278
err_2	10.61728	20.29393	40.2572

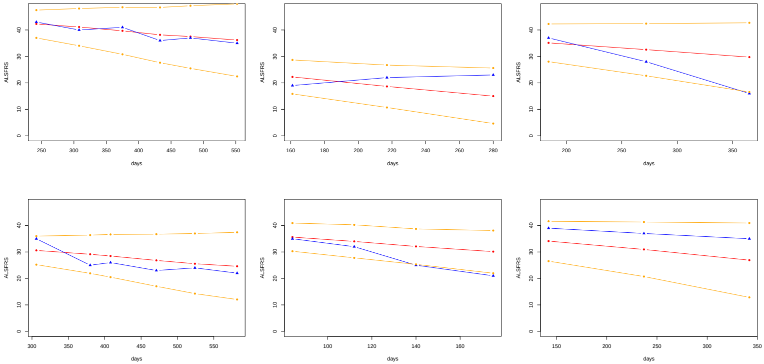
Final Model

	Training set	Train with new obs.	Test set
err_1	1.048792	3.582663	5.977326
err_2	9.024221	20.45746	35.94814

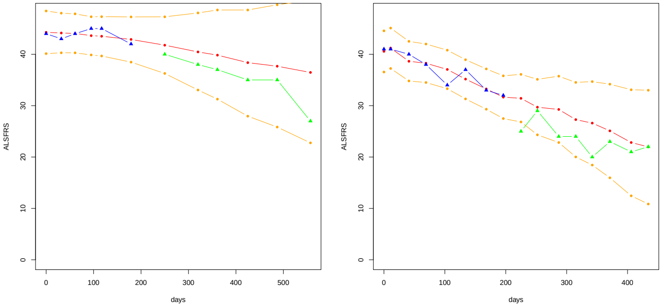
Prediction on the training set



Prediction on train_patient_test_obs

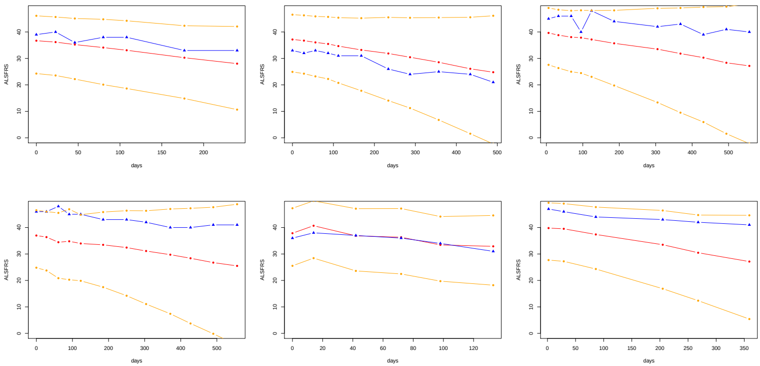


Prediction on train_patient_test_obs



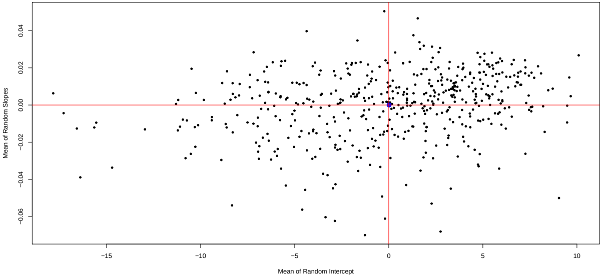
Two examples of patient in the train (blue points) and train_patient_test_obs (green points).

Prediction on test set



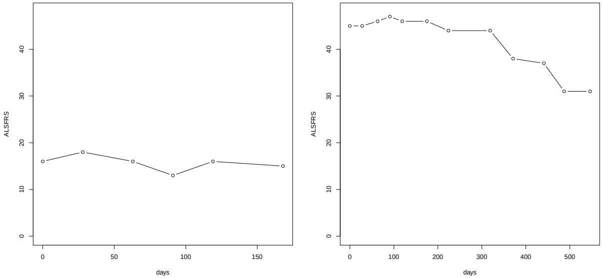
Variability among patients

We plotted the pairs of the random effect's means and we looked for patients with large distance from the null point. One example is:



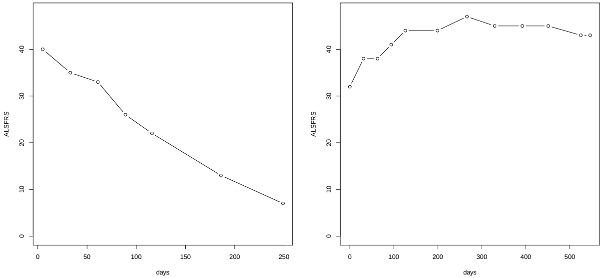
Mean random intercept vs mean random slope

Variability among patients: intercept



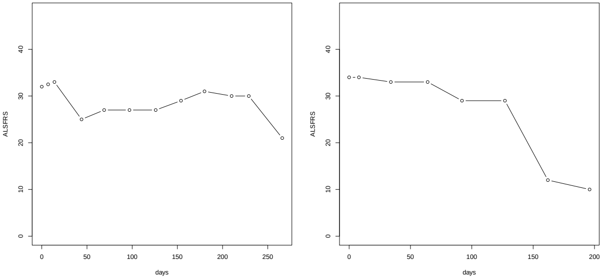
Patients with minimum (left) and maximun (right) mean random intercept.

Variability among patients: slope



Patients with minimum (left) and maximun (right) mean random slope.

Variability among patients: cos_1



Patients with minimum (left) and maximun (right) mean random cos_1.

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