Lung Cancer Survival Prediction with Bayesian Generalised Linear Models



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1 Introduction

Lung cancer is one of the most common types of cancer for both men and women. The exploration of survival of patients with lung cancer is crucial for controlling the disease development, obtaining right treatment methods, understanding what influences the disease progression. To accomplish these purposes, accurate survival analysis methods are needed.

Survival analysis is the combination of different statistical methods for analyzing time to event data. Exploring survival models can be challenging, since different models from non-parametric to parametric can be used, various distributions, like exponential, Weibull, log-normal, are applicable for each concrete case. The most common model is Cox hazard model, however, it is too simple and proposes constant effect of predictor variables on survival duration throughout time.

This study examines the way Bayesian approach proceeds to fit Weibull model for lifetime data of patients with advanced lung cancer analysis. Weibull approach is more flexible and hazard rate is not constant through time. For simulation Bayesian inference with MCMC is used, providing us with satisfying approximation of uncertainty and ability to use priors as domain knowledge. The model is implemented and tested with the help of R and Stan package.

The code with model implementation is provided in McLatchie and Odnoblyudova [2021].

1.1 Data description

1.1.1 General description

The data used in the study shows survival of patients with advanced lung cancer from the North Central Cancer Treatment Group. It is provided in the survival R package, Therneau [2021].

1.1 Data description 1 INTRODUCTION

The problem, tring to be solved, is connected with the prediction of survival time of patients with lung cancer.

Dataset contains 9 features and 228 observations, which are assumed to be independent and identically distributed. The target variable is the survival time in days. The covariates are presented by both categorical and numerical values.

Special attention has to be paid for "censoring status" feature. It indicates if the patient had an event (=1) or not (=0). If patient is censored, true survival time for him is not known. Right censoring approach is used, meaning incompleteness of survival time at the right side of the follow-up period. We can get rid of it.

There are three variables, needed to be explained: ph.ecog - ECOG performance score (0-4). 0-good condition, 4-the worst condition, much time in bad. ph.karno - Karnofsky performance score (bad=0-good=100). Provided by physician. pat.karno - Karnofsky performance score. Provided by patient.

1.1.2 Exploratory data analysis

It is better to provide some descriptive statistics to familiarize with data.

```
library(dplyr)
library(ggplot2)
data("cancer", package = "survival")
```

There were 61 observations with missed values, which have been removed from dataset. Now it consists of 167 rows.

```
data = cancer %>% na.omit()
```

Institutions are considered as variables, useful for hierarchical model.

```
table(data$inst)
```

```
## ## 1 2 3 4 5 6 7 10 11 12 13 15 16 21 22 26 32 ## 28 4 12 4 7 12 7 4 13 16 13 6 10 8 13 4 6
```

Moving to categorical variables (fig.1), the number of men prevails over women. The majority of patients are ambulatory with symptoms.

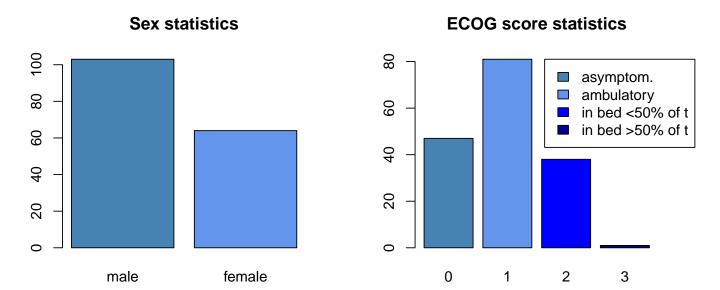
The distribution for continuous variables is shown in fig. 2. The features do not follow normal distribution.

```
par(mfrow=c(3,2))
hist(data$age, freq=FALSE, col="cornflowerblue", main="Histogram of age",xlab="")
hist(data$ph.karno, freq=FALSE, col="cornflowerblue", main="Histogram of ph.karno",xlab="")
hist(data$pat.karno, freq=FALSE, col="cornflowerblue", main="Histogram of pat.karno",xlab="")
hist(data$meal.cal, freq=FALSE, col="cornflowerblue", main="Histogram of meal.cal",xlab="")
hist(data$wt.loss, freq=FALSE, col="cornflowerblue", main="Histogram of wt.loss",xlab="")
```

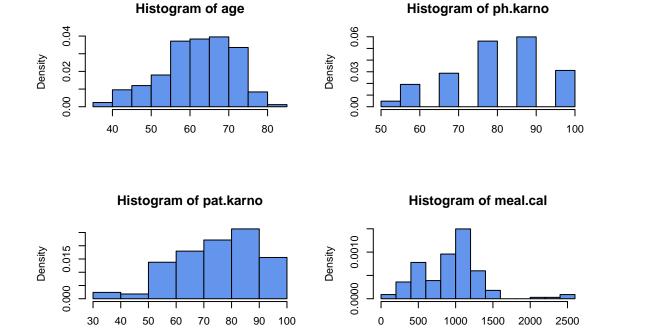
It is also useful to identify if there is linear correlation between variables. The correlation is not that high, the only one is between ph.karno and pat.karno (0.525), but it is reasonable, as, eventually, patient and doctor measure the same quantity.

```
cor(data[c(4,7,8,9,10)], method=c("pearson"))
```

1.1 Data description 1 INTRODUCTION



 $Figure \ 1: \ Categorical \ variables$



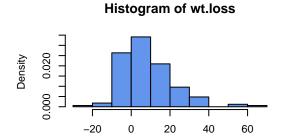


Figure 2: Continuous variables

```
##
                            ph.karno pat.karno
                                                   meal.cal
                                                                wt.loss
                     age
## age
              1.00000000 -0.32261297 -0.2398974 -0.23958240
                                                            0.04286056
                                                 0.05385409 -0.12524032
## ph.karno -0.32261297
                          1.00000000
                                      0.5350275
## pat.karno -0.23989736
                         0.53502749
                                      1.0000000
                                                 0.17465190 -0.18213953
## meal.cal
            -0.23958240
                         0.05385409
                                      0.1746519
                                                 1.00000000 -0.11134425
## wt.loss
              0.04286056 -0.12524032 -0.1821395 -0.11134425 1.00000000
```

1.2 Relative studies

The original data was presented in the work Loprinzi et al. [1994] in 1994, it just provided descriptive information from a lung patient-completed questionnaire, which was aggregated into dataset. In ? the comparison of semi-parametric and non-parametric models for survival analysis was presented, but different dataset was used, also there was no deep description of Weibull model implementation, i.e. more attention was payed to Cox regression. Study Abujarad and Khan [2018] provided the description of exponential models, applied to lung cancer data analysis with Stan code. The Weibull distribution was just mentioned their as a possibility, but no formulas and conclusions were derived for Weibull model. That is why in that work two Weibull Survival models are built: hierarchical and non-hierarchical. The main approaches and theory of building survival models were used from the studies above, but the stan implementation, priors choice was made by the authors.

2 Description of models

In the following section, we will motivate and define mathematically four Generalised Linear Models (GLMs) implemented in Stan and using BRMS in two cases.

```
# install libraries
library(survival)
library(tidyverse)
## -- Attaching packages -----
                                               ----- tidyverse 1.3.1 --
## v tibble 3.1.6
                               0.3.4
                      v purrr
## v tidyr
            1.1.4
                      v stringr 1.4.0
## v readr
            2.0.2
                      v forcats 0.5.1
## -- Conflicts ----- tidyverse_conflicts() --
## x dplyr::filter() masks stats::filter()
## x dplyr::lag()
                    masks stats::lag()
library(rstan)
## Loading required package: StanHeaders
## rstan (Version 2.21.2, GitRev: 2e1f913d3ca3)
## For execution on a local, multicore CPU with excess RAM we recommend calling
## options(mc.cores = parallel::detectCores()).
## To avoid recompilation of unchanged Stan programs, we recommend calling
## rstan_options(auto_write = TRUE)
##
## Attaching package: 'rstan'
  The following object is masked from 'package:tidyr':
##
##
      extract
```

```
library(brms)
## Loading required package: Rcpp
## Loading 'brms' package (version 2.16.1). Useful instructions
## can be found by typing help('brms'). A more detailed introduction
## to the package is available through vignette('brms_overview').
##
## Attaching package: 'brms'
## The following object is masked _by_ '.GlobalEnv':
##
##
       kidney
## The following object is masked from 'package:rstan':
##
##
       100
## The following object is masked from 'package:survival':
##
##
       kidney
## The following object is masked from 'package:stats':
##
       ar
library(bayesplot)
## This is bayesplot version 1.8.1
## - Online documentation and vignettes at mc-stan.org/bayesplot
## - bayesplot theme set to bayesplot::theme_default()
##
      * Does _not_ affect other ggplot2 plots
      * See ?bayesplot_theme_set for details on theme setting
##
library(loo)
## This is loo version 2.4.1
## - Online documentation and vignettes at mc-stan.org/loo
## - As of v2.0.0 loo defaults to 1 core but we recommend using as many as possible. Use the 'cores' argum
##
## Attaching package: 'loo'
## The following object is masked from 'package:rstan':
##
##
       100
library(reshape2)
##
## Attaching package: 'reshape2'
## The following object is masked from 'package:tidyr':
##
##
       smiths
```

```
library(ggplot2)
library(splines2)
# set number of cores
options(mc.cores = parallel::detectCores())
# read lung cancer data from `survival` library
data("cancer", package = "survival")
# build dataset from only those non-censored data points
uncensored data <- cancer %>%
  filter(status == 2) %>%
  drop_na()
# identify covariate labels and build design matrix
cov labels <- uncensored data %>%
  dplyr::select(-status,-time,-inst) %>%
  colnames()
# build design matrix
X <- as.matrix(uncensored_data[cov_labels])</pre>
# print(dim(X))
# [1] 120
y <- uncensored_data$time
# build data list for Stan model
weibull_data = list(
  y = y, X = X, N = length(y), M = ncol(X)
```

2.1 Weibull without censored data

Let $y \sim \text{Weibull}(\alpha, \sigma)$, so that

Weibull
$$(y|\alpha,\sigma) = \frac{\alpha}{\sigma} \left(\frac{y}{\sigma}\right)^{\alpha-1} \exp\left(-\left(\frac{y}{\sigma}\right)^{\alpha}\right)$$
,

for $y \in [0, \infty), \alpha \in \mathbb{R}^+$, and $\sigma \in \mathbb{R}^+$.

2.1.1 Motivating the distribution

The Weibull distribution is often used as a more flexible and complex alternative to the semi-parametric proportional hazard Cox model for modelling time to failure events, since the hazard rate is not taken to be constant with time.

2.1.2 The Weibull distribution as a member of the exponential family

Now take α fixed and finite, then it can be shown that this distribution belongs to the exponential family since we can write it's probability density function

Weibull
$$(y|\sigma) = \alpha y^{\alpha-1} \exp(-y^{\alpha} \sigma^{-\alpha} - \alpha \log \sigma),$$

with

$$b(y) = \alpha y^{\alpha - 1}$$
$$\eta = \sigma^{-\alpha}$$
$$T(y) = -y^{\alpha}$$
$$a(\eta) = \alpha \log \sigma.$$

2.1.3 Defining the link function

Looking at our sufficient statistic $\eta = \sigma^{-\alpha}$, it can be shown that

$$\sigma = \exp\left(\frac{\log \eta}{-\alpha}\right)$$

where we construct $\eta = \exp(\mathbf{X}\beta)$ so that η is strictly positive. Thus we choose a log link function for our GLM such that

$$\sigma = \exp(-\frac{X\beta}{\alpha}).$$

2.1.4 **Priors**

print(wm)

In our Stan model, we will enforce two priors over each of the regressors in the linear model, and the shape parameter of our resulting Weibull distribution. Mathematically,

$$\beta \sim N(0, 10)$$

 $\alpha \sim \text{Half-Cauchy}(5),$

as is motivated in Gelman [2006]. In this pooled model, we model these parameters the same across all institutions. Intuitively, this means that we expect the hazard to be equivalent regardless of which institution a patient is in.

2.1.5 Implemented in Stan

Below, we fit the model in Stan and output the Stan code for the reader.

```
# compile and run seperate model
wm <- rstan::stan_model(file = "../stan/weibull_survival.stan")</pre>
FALSE Running /anaconda3/envs/seurat4/lib/R/bin/R CMD SHLIB foo.c
FALSE x86_64-apple-darwin13.4.0-clang -I"/anaconda3/envs/seurat4/lib/R/include" -DNDEBUG
                                                                                            -I"/anaconda3/e
FALSE In file included from <built-in>:1:
FALSE In file included from /anaconda3/envs/seurat4/lib/R/library/StanHeaders/include/stan/math/prim/mat/f
FALSE In file included from /anaconda3/envs/seurat4/lib/R/library/RcppEigen/include/Eigen/Dense:1:
FALSE In file included from /anaconda3/envs/seurat4/lib/R/library/RcppEigen/include/Eigen/Core:88:
FALSE /anaconda3/envs/seurat4/lib/R/library/RcppEigen/include/Eigen/src/Core/util/Macros.h:628:1: error: u
FALSE namespace Eigen {
FALSE ^
FALSE /anaconda3/envs/seurat4/lib/R/library/RcppEigen/include/Eigen/src/Core/util/Macros.h:628:16: error:
FALSE namespace Eigen {
FALSE
FALSE
FALSE In file included from <built-in>:1:
FALSE In file included from /anaconda3/envs/seurat4/lib/R/library/StanHeaders/include/stan/math/prim/mat/f
FALSE In file included from /anaconda3/envs/seurat4/lib/R/library/RcppEigen/include/Eigen/Dense:1:
FALSE /anaconda3/envs/seurat4/lib/R/library/RcppEigen/include/Eigen/Core:96:10: fatal error: 'complex' fil
FALSE #include <complex>
FALSE
FALSE 3 errors generated.
FALSE make: *** [/anaconda3/envs/seurat4/lib/R/etc/Makeconf:174: foo.o] Error 1
# print out Stan code
```

```
FALSE S4 class stanmodel 'weibull_survival' coded as follows:
FALSE data {
FALSE
        int<lower=0> N; // number of data realisations
        int<lower=0> M; // feature dimensionality
FALSE
FALSE
      vector<lower=0>[N] y; // survival time
FALSE matrix[N, M] X; // design matrix
FALSE }
FALSE
FALSE transformed data {
       matrix[N, M] Xc; // centered version of X without an intercept
FALSE
FALSE
        vector[M] means_X; // column means of X before centering
FALSE
FALSE
       // column-center the design matrix for fitting the model
FALSE for (m in 1:M) {
FALSE
         means_X[m] = mean(X[, m]);
FALSE
          Xc[, m] = X[, m] - means_X[m];
FALSE
FALSE }
FALSE
FALSE parameters {
FALSE // GLM parameters
      vector[M] beta; // regressors
FALSE
        real<lower=0> alpha; // shape parameter
FALSE }
FALSE
FALSE transformed parameters {
FALSE // compute latent predictor term
      vector[N] eta = Xc * beta;
FALSE
FALSE
       // apply the log inverse link function
FALSE
        vector<lower=0>[N] sigma = exp(-eta / alpha);
FALSE }
FALSE
FALSE model {
FALSE
       // prior over regressor and shape parameters
FALSE
       beta ~ normal(0, 1);
FALSE alpha ~ cauchy(0, 5);
FALSE
FALSE
       // fit model
       y ~ weibull(alpha, sigma);
FALSE
FALSE }
FALSE
FALSE generated quantities {
FALSE // compute predictive distribution for survival time
FALSE
        real ypred[N] = weibull_rng(alpha, sigma);
FALSE
FALSE
        // log-likelihood
FALSE
       vector[N] log_lik;
FALSE
        for (n in 1:N) {
FALSE
          log_lik[n] = weibull_lpdf(y[n] | alpha, sigma[n]);
FALSE
FALSE }
# learn the model parameters
weibull_model <- rstan::sampling(</pre>
```

```
wm,
iter = 10000,
data = weibull_data
)
```

2.2 Weibull with censored data

2.2.1 Implemented in Stan

2.3 Hierarchical Weibull without censored data

Here we implement a model with some global shape parameter to be learned, but independent regressor parameters for each institution. Once more, we ignore the censored data. By virtue of this, we need not worry about complex distribution functions, but do sacrifice the number of data points we can learn from for each institution.

2.3.1 Defining the link function

2.3.2 Priors

The same priors are used for the hierarchical model as the pooled model

2.3.3 Implemented in BRMS

```
FALSE // generated with brms 2.16.1
FALSE functions {
FALSE /* compute correlated group-level effects
FALSE
        * Args:
FALSE
            z: matrix of unscaled group-level effects
FALSE
            SD: vector of standard deviation parameters
FALSE
            L: cholesky factor correlation matrix
FALSE
        * Returns:
FALSE
            matrix of scaled group-level effects
FALSE
        */
FALSE
        matrix scale_r_cor(matrix z, vector SD, matrix L) {
FALSE
         // r is stored in another dimension order than z
FALSE
          return transpose(diag_pre_multiply(SD, L) * z);
```

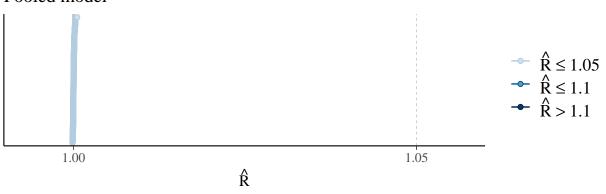
```
FALSE
FALSE }
FALSE data {
        int<lower=1> \mathbb{N}; // total number of observations
FALSE
FALSE
       vector[N] Y; // response variable
FALSE
        // data for group-level effects of ID 1
FALSE
       int<lower=1> N 1; // number of grouping levels
        int<lower=1> M_1; // number of coefficients per level
FALSE
        int<lower=1> J_1[N]; // grouping indicator per observation
FALSE
       // group-level predictor values
FALSE
FALSE
       vector[N] Z_1_1;
      vector[N] Z_1_2;
FALSE
      vector[N] Z_1_3;
FALSE
FALSE vector[N] Z_1_4;
FALSE
       vector[N] Z_1_5;
FALSE
       vector[N] Z_1_6;
FALSE vector[N] Z_1_7;
FALSE
       vector[N] Z 1 8;
        int<lower=1> NC_1; // number of group-level correlations
FALSE
FALSE
        int prior_only; // should the likelihood be ignored?
FALSE }
FALSE transformed data {
FALSE }
FALSE parameters {
       real Intercept; // temporary intercept for centered predictors
FALSE
       real<lower=0> shape; // shape parameter
FALSE
       vector<lower=0>[M_1] sd_1; // group-level standard deviations
FALSE
       matrix[M_1, N_1] z_1; // standardized group-level effects
FALSE
        cholesky_factor_corr[M_1] L_1; // cholesky factor of correlation matrix
FALSE }
FALSE transformed parameters {
FALSE matrix[N_1, M_1] r_1; // actual group-level effects
FALSE
       // using vectors speeds up indexing in loops
FALSE vector[N_1] r_1_1;
FALSE
       vector[N_1] r_1_2;
FALSE vector[N_1] r_1_3;
FALSE vector[N_1] r_1_4;
FALSE vector[N_1] r_1_5;
FALSE vector[N_1] r_1_6;
FALSE vector[N_1] r_1_7;
FALSE
       vector[N_1] r_1_8;
FALSE
       // compute actual group-level effects
FALSE
       r_1 = scale_r_cor(z_1, sd_1, L_1);
      r_1_1 = r_1[, 1];
FALSE
FALSE r_1_2 = r_1[, 2];
FALSE
       r_1_3 = r_1[, 3];
FALSE
       r_1_4 = r_1[, 4];
FALSE
       r_1_5 = r_1[, 5];
FALSE
       r_1_6 = r_1[, 6];
       r_1_7 = r_1[, 7];
FALSE
FALSE
       r_1_8 = r_1[, 8];
FALSE }
FALSE model {
FALSE // likelihood including constants
```

```
FALSE
               if (!prior_only) {
FALSE
                   // initialize linear predictor term
FALSE
                   vector[N] mu = Intercept + rep_vector(0.0, N);
FALSE
                   for (n in 1:N) {
FALSE
                       // add more terms to the linear predictor
                       mu[n] += r_1_1[J_1[n]] * Z_1_1[n] + r_1_2[J_1[n]] * Z_1_2[n] + r_1_3[J_1[n]] * Z_1_3[n] + r_1_3[J_1[n]] * Z_1[n] * Z_1
FALSE
FALSE
                   }
FALSE
                   for (n in 1:N) {
FALSE
                       // apply the inverse link function
FALSE
                       mu[n] = exp(mu[n]) / tgamma(1 + 1 / shape);
FALSE
FALSE
                   target += weibull_lpdf(Y | shape, mu);
FALSE
FALSE
               // priors including constants
               target += student_t_lpdf(Intercept | 3, 5.5, 2.5);
FALSE
FALSE
               target += cauchy_lpdf(shape | 0, 5)
FALSE
                   -1 * cauchy_lccdf(0 | 0, 5);
FALSE
               target += normal_lpdf(sd_1 | 0, 1)
FALSE
                   - 8 * normal_lccdf(0 | 0, 1);
FALSE
               target += std_normal_lpdf(to_vector(z_1));
FALSE
               target += lkj_corr_cholesky_lpdf(L_1 | 1);
FALSE }
FALSE generated quantities {
FALSE
               // actual population-level intercept
FALSE
               real b_Intercept = Intercept;
FALSE
               // compute group-level correlations
FALSE
               corr_matrix[M_1] Cor_1 = multiply_lower_tri_self_transpose(L_1);
               vector<lower=-1,upper=1>[NC_1] cor_1;
FALSE
FALSE
               // extract upper diagonal of correlation matrix
FALSE
               for (k in 1:M_1) {
FALSE
                   for (j in 1:(k-1)) {
FALSE
                       cor_1[choose(k - 1, 2) + j] = Cor_1[j, k];
FALSE
                   }
FALSE
               }
FALSE }
# fit hierarchical GLM model with BRMS, expliciting a non-exponential family
weibull_hier <- brm(</pre>
   formula = hw_formula,
   data = uncensored_data,
    prior = hw_prior,
   family = weibull(link = "log", link_shape = "log"),
   iter = 10000,
    cores = parallel::detectCores()
)
FALSE Running /anaconda3/envs/seurat4/lib/R/bin/R CMD SHLIB foo.c
FALSE x86_64-apple-darwin13.4.0-clang -I"/anaconda3/envs/seurat4/lib/R/include" -DNDEBUG
                                                                                                                                                                               -I"/anaconda3/e
FALSE In file included from <built-in>:1:
{\tt FALSE~In~file~included~from~/anaconda3/envs/seurat4/lib/R/library/StanHeaders/include/stan/math/prim/mat/files/respectively.} \\
FALSE In file included from /anaconda3/envs/seurat4/lib/R/library/RcppEigen/include/Eigen/Dense:1:
FALSE In file included from /anaconda3/envs/seurat4/lib/R/library/RcppEigen/include/Eigen/Core:88:
FALSE /anaconda3/envs/seurat4/lib/R/library/RcppEigen/include/Eigen/src/Core/util/Macros.h:628:1: error: u
FALSE namespace Eigen {
FALSE ^
```

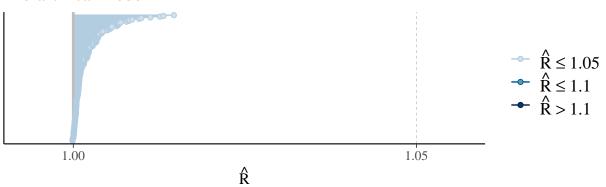
3 Diagnostics and performance

3.1 \hat{R} , effective sample size, and divergences

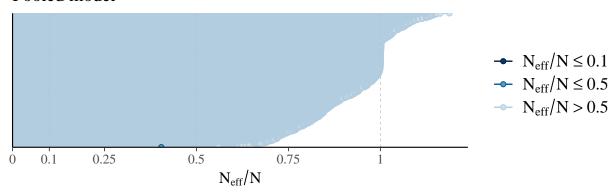
Pooled model



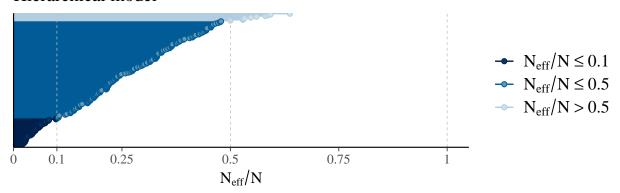
Hierarchical model



Pooled model



Hierarchical model



3.2 Posterior predictive checks

3.3 Model comparison using leave-one-out cross-validation and WAIC

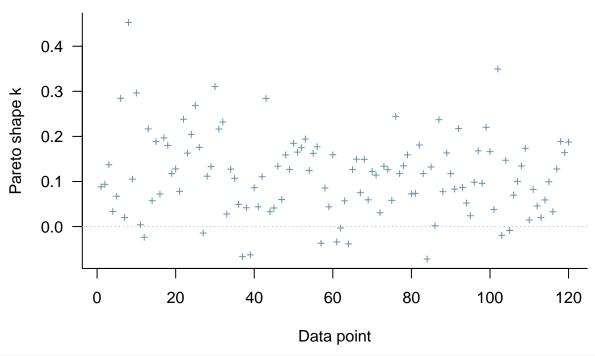
```
# perform approximate loo and psis-loo
wm_log_lik <- extract_log_lik(weibull_model, merge_chains = FALSE)
# estimate the PSIS effective sample size
wm_r_eff <- relative_eff(exp(wm_log_lik), cores = parallel::detectCores())
# compute loo
wm_loo <- loo(wm_log_lik, r_eff = wm_r_eff, cores = parallel::detectCores())
# compute waic
wm_waic <- waic(wm_log_lik, cores = parallel::detectCores())
# repeat for hierarchical Weibull
hwm_loo <- loo(weibull_hier, cores = parallel::detectCores())
## Warning: Found 4 observations with a pareto_k > 0.7 in model 'weibull_hier'. It
## is recommended to set 'moment_match = TRUE' in order to perform moment matching
## for problematic observations.
hwm_waic <- waic(weibull_hier, cores = parallel::detectCores())</pre>
```

Warning:

14 (11.7%) p_waic estimates greater than 0.4. We recommend trying loo instead. # $plot\ pareto\ k\ diagnostics\ for\ the\ models$

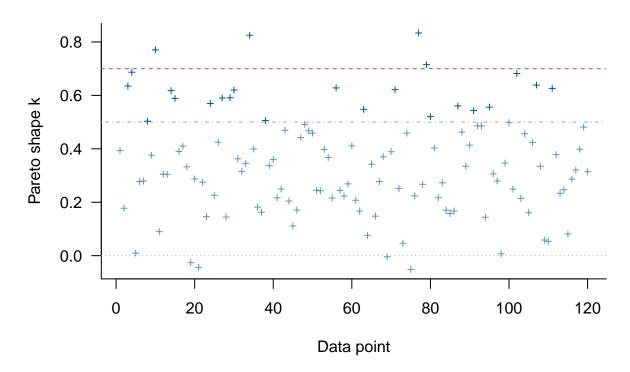
plot(wm_loo)

PSIS diagnostic plot



plot(hwm_loo)

PSIS diagnostic plot



```
# comparison of models with loo
loo_compare(x = list(wm_loo, hwm_loo))
## Warning: Not all models have the same y variable. ('yhash' attributes do not
## match)
##
                elpd_diff se_diff
## weibull hier
                   0.0
                              0.0
## model1
                 -253.4
                             10.1
# comparison of models with waic
loo_compare(x = list(wm_waic, hwm_waic))
## Warning: Not all models have the same y variable. ('yhash' attributes do not
  match)
##
                elpd_diff se_diff
                              0.0
## weibull_hier
                   0.0
## model1
                 -255.3
                             10.0
```

4 Conclusion

4.1 Issues and improvements

The problem may be that the distribution is rather skewed. Therefore, it is rather difficult to choose for it a competent distribution. Maybe in the future it'd be better to try one more distribution - gamma or such extensions of exponential, like: exponentialed exponential (has properties, similar to Gamma distribution, but survival function like a Weibull).

Also, maybe it'd be worth to pay more attention to features and apply transformation or even extraction to them. Moreover, the priors can be tested even more accurately, variant like half-cauchy can be tried.

4.2 Self-reflection and learnings

The group learnt a lot about the applications of MCMC methods to Survival analysis. Previously, some of us did not even know about the concept of Survival analysis, about such terms, like survival, hazard function, or with what distributions survival time can be simulated. Also, previously, there wasn't chance to dive deep into the Weibull regression models, now degree of understanding of this model increased. Last but not least, some functions in R were discovered (connected with bayesian statistics), about which have never heard before.

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