Workbook for Introduction to TTE modeling

Integrating the hazard funtion in Stan

2022-08-31

Contents

Preliminaries for R examples

```
library(tidyverse)
library(stringr)
library(survival)
library(survminer)
library(texreg)
library(mgcv)
library(muhaz)
library(rstan)
library(bayesplot)
library(tidybayes)

theme_set(theme_bw())
bayesplot::color_scheme_set("viridis")
```

```
# OS data
d <- read_csv('../data/source/DDmodel0218_Simulated_OS.csv', na = c('.','-99'))

# Add week 12 (Day 84) predicted tumor size
d84 <- d %>%
  filter(TIME <= 84) %>%
  group_by(ID) %>%
  mutate(rate = KG/1000 - KD0/1000*AUC0 - KD1/100*AUC1,
         prevTIME = lag(TIME,default = 0),
         change = exp(rate * (TIME-prevTIME)),
         ipred = IBASE * 1000 * cumprod(change)
         ) %>%
  arrange(ID,TIME) %>%
  slice(n()) %>%
  mutate(ipred84 = ipred * exp(rate * (84-TIME)),
         rts84 = ipred84 / ( IBASE * 1000 ) )

dos <- d %>%
  filter(TIME>0) %>%
```

```r
  group_by(ID) %>%
  mutate(meanGem = mean(AUC1),
         Group = if_else(meanGem > 0, "Cb+G", "Cb")) %>%
  ungroup() %>%
  filter(CMT==2, EVID==0) %>%
  left_join(d84 %>% select(ID, ipred84, rts84)) %>%
  mutate(rts84_f = paste0("Q", ntile(rts84, n = 4)))

dos84 <- dos %>%
  filter(TIME>84) %>%
  mutate(TIME = TIME-84)
```

Working with traditional pharmacometric parameterization of Weibull model

$$
\begin{aligned}
h_i(t) &= h_0(t) \times \exp(\beta \times \mathrm{RTS}_i) \\
h_0(t) &= \lambda_0 \times \alpha \ \ \times t^{\alpha-1} \\
\\
H_i(t) &= \lambda_i t^{\alpha} \\
S_i(t) &= \exp(-\lambda_i t^{\alpha})
\end{aligned}
$$

Under this parameterization,

- median OS $= \left(\frac{\log 2}{\lambda_0 \exp(\beta \times RTS)}\right)^{1/\alpha}$
- mean OS $= \{\lambda_0 \exp(\beta \times RTS)\}^{-1/\alpha} \quad \Gamma(1 + 1/\alpha)$

Set-up the data

```r
tte_emax_data <- list(
  N = nrow(dos84),
  Y = dos84$TIME/365,  # Use years instead of days
  cens = 1-dos84$DV,
  K = 1,
  X = model.matrix(~-1 + ECOG, data=dos84),
  RTS = dos84$rts84,
  prior_only = 0
)
```

```r
fit_weibull_int <- stan(file = '../model/stan/weibull_integrated_hazard.stan',
                        data = tte_emax_data,
                        chains = 4,
                        iter=1000,
                        cores = 4,
                        seed = 76341
                        )
```

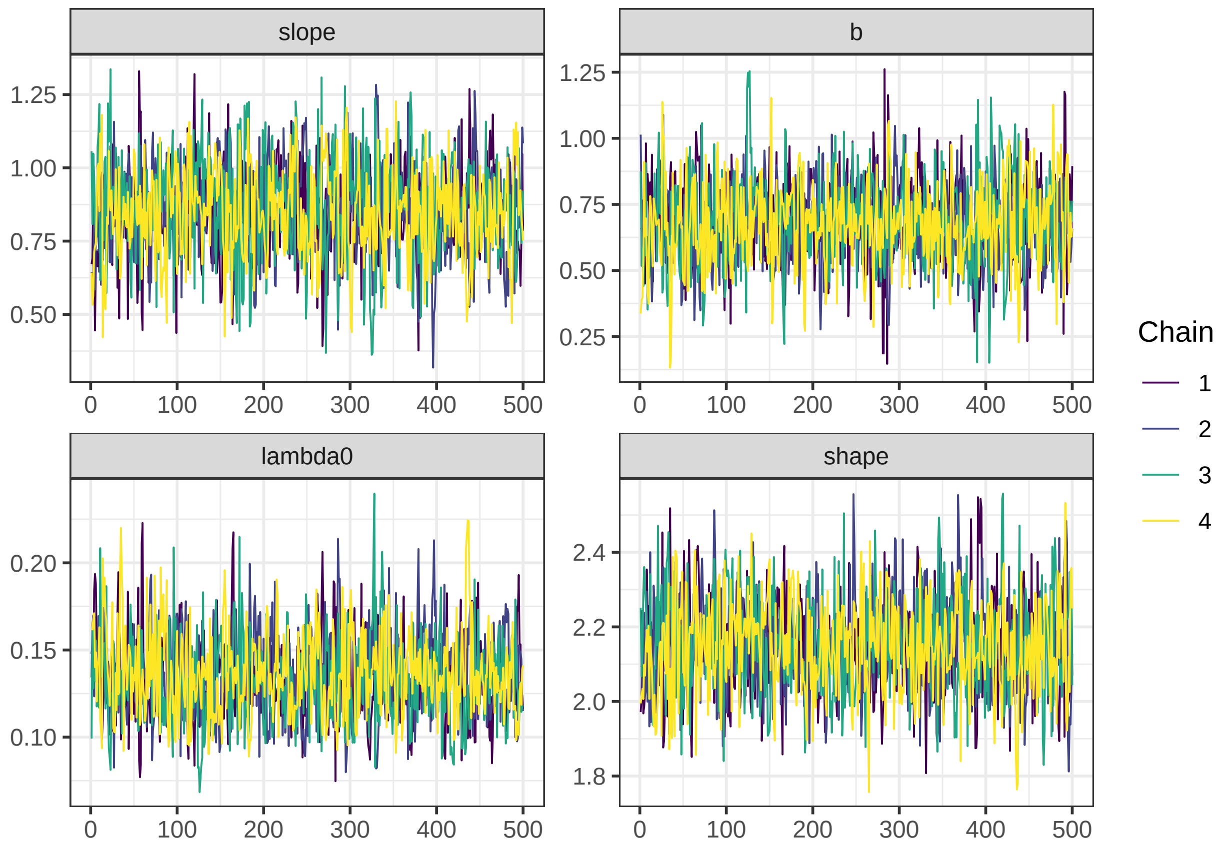
```r
print(fit_weibull_int, pars=c('slope','lambda0','b','shape'))
```

```
. Inference for Stan model: weibull_integrated_hazard.
. 4 chains, each with iter=1000; warmup=500; thin=1;
. post-warmup draws per chain=500, total post-warmup draws=2000.
.
```

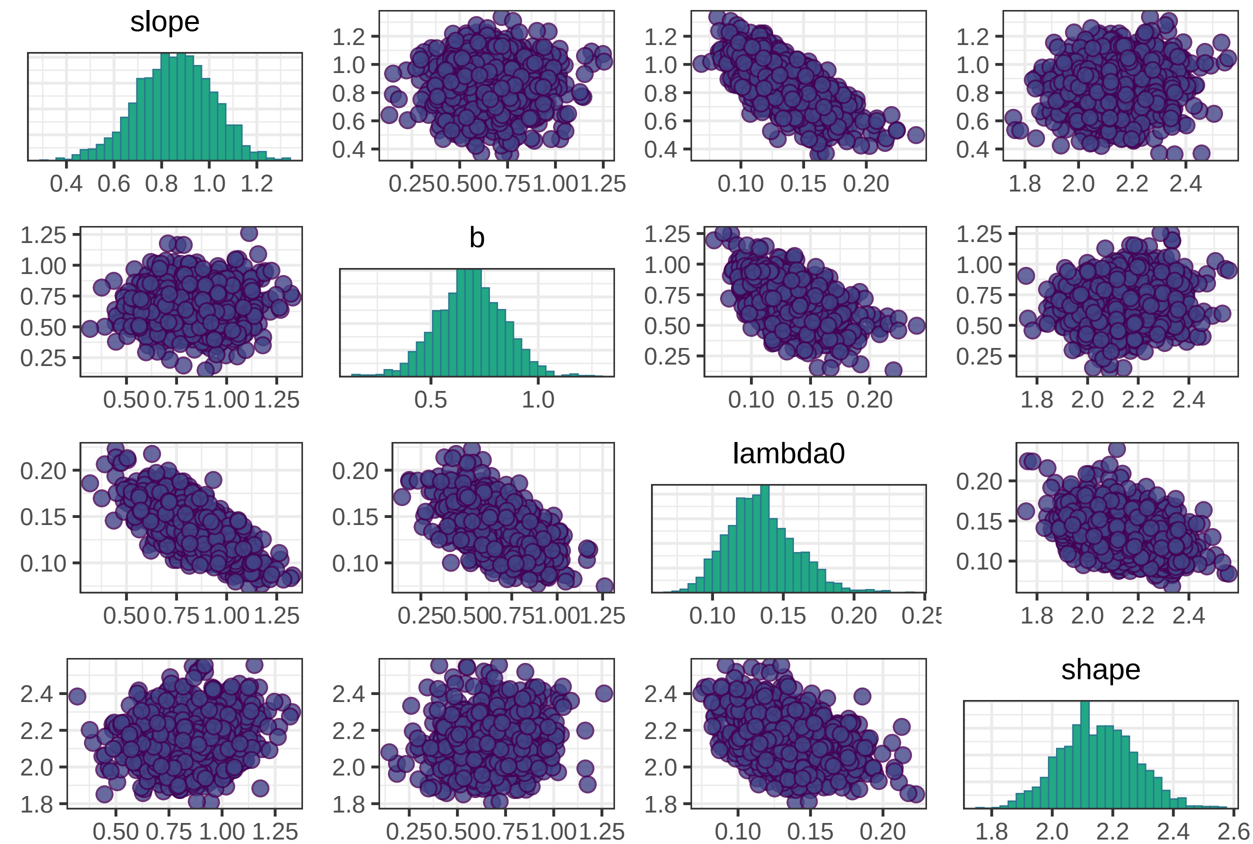
```
.          mean se_mean   sd 2.5%  25%  50%  75% 97.5% n_eff Rhat
. slope    0.86       0 0.16 0.53 0.75 0.86 0.96  1.15  1091    1
. lambda0 0.13       0 0.02 0.09 0.12 0.13 0.15  0.19   975    1
. b[1]     0.68       0 0.16 0.38 0.58 0.68 0.79  0.98  1340    1
. shape    2.15       0 0.13 1.91 2.07 2.15 2.24  2.40  1091    1
.
. Samples were drawn using NUTS(diag_e) at Wed Aug 31 22:19:28 2022.
. For each parameter, n_eff is a crude measure of effective sample size,
. and Rhat is the potential scale reduction factor on split chains (at
. convergence, Rhat=1).
```

```
samples_int <- spread_draws(fit_weibull_int, slope,b[i],lambda0,shape) %>%
  rename(Chain=.chain)
```

```
mcmc_trace(samples_int, pars=c('slope','b','lambda0','shape'))
```




```
mcmc_pairs(samples_int, pars=c('slope','b','lambda0','shape'))
```



** Exercise: **

How does this compare to the closed-form model? Re-fit the closed-form model and compare parameter estimates.

Try coding a model with a 'hockey stick' hazard:

$$h(t) = \begin{cases} \alpha_1 + \beta_1 t & 0 \leq t < \tau_1 \\ \alpha_1 + \beta_1 \tau_1 + \beta_2 (t - \tau_1) & t \geq \tau_1 \end{cases}$$

where you can either pick a fixed value of τ_1 or estimate it.

How does this compare to the Weibull model fit?