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On Bayesian Analysis of the Proportional Hazards Model

Sull'Analisi Bayesiana del Modello a Rischi Proporzionali

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The proportional hazards model

It is a well known model for regression in survival analysis, introduced by Cox (1972), in which

$T_1, \ldots, T_N$ are the survival times of interest

$x_1, \ldots, x_N$ are the corresponding vectors of covariates

the unknown distribution of T_i is described through its hazard rate

$$\rho_i(t) = \lim_{h \downarrow 0} \frac{1}{h} \mathcal{P}(t \leq T_i \leq t + h \mid T_i \geq t), \quad t \in \mathbb{R}_+, \quad i = 1 \ldots N$$

and it is assumed that this can be factored as

$$\rho_i = e^{<\beta, x_i>} \rho_\star, \quad i = 1 \ldots N$$

where e is the basis of the natural logarithms and $\langle \cdot, \cdot \rangle$ denotes the ordinary scalar product, say in $\mathbb{R}^p$.

Analysis of the proportional hazards model

Interest lies in estimating both

- the vector of regression parameters β

- and the so-called baseline hazard rate $\rho_\star$

from possibly right censored observations, that is having observed an event of the form

$$\{T_1 = t_1, T_2 > t_2\}$$

where, for simplicity, the case $N = 2$ has been considered. It is assumed that the censoring mechanism be non-informative.

Bayesian analysis of the proportional hazards model

First, a joint prior distribution on β and $\rho_\star$ needs to be elicitated.

This can be done by building a stochastic process $\rho_\star$ such that

$$\rho_\star \geq 0, \quad \int_0^t \rho_\star(s)ds < \infty, \quad \int_0^\infty \rho_\star(s)ds = \infty$$

together with a random vector β on a suitable probability space.

Then, the corresponding posterior distribution has to be computed.

The Bayes formula based on the standard likelihood

$$\mathscr{L}(t \mid o, x; \rho_\star, \beta) = \prod_{i=1}^{N} \left[e^{<\beta, x_i>} \rho_\star(t_i)\right]^{o_i} \exp\left\{-e^{<\beta, x_i>} \int_0^{t_i} \rho_\star(s)\, ds\right\}$$

where $o_i = 1$, if t_i is exact, and $o_i = 0$, if t_i is right censored,
can be approximated by means of *ad hoc* MCMC techniques.

Proportional hazards without the hazard rate

An alternative definition of the proportional hazards model is given by the formula

$$\log \Sigma_i(t) = e^{<\beta,x_i>} \log \Sigma_\star(t), \quad t \in \mathbb{R}_+$$

which relates the unknown survival function Σ_i of the $i-$th survival time to the baseline survival function $\Sigma_\star$.

Note that the above formula does not require the hazard rate to be defined.

- Kalbfleisch (1978) built $-\log \Sigma_\star$ as a gamma process and estimated β by maximizing its marginal likelihood

- Hjort (1990) built $-\int_{[0,\cdot]} \Sigma_{\star-}^{-1}(t)\Sigma_\star(dt)$ as a beta process and suggested simulation techniques alternatively to the empirical Bayes approach

Building the prior hazard rate

An infinitely smooth possibility (La Rocca, 2003) is to take

$$\rho_\star(t) = q[1 - K(t)]\xi_0 + \sum_{j=1}^{\infty} \xi_j k(t - \sigma_j), \qquad t \in \mathbb{R}_+$$

where

$\xi_0, \xi_1, \xi_2, \ldots \overset{i.i.d.}{\sim} \mathcal{G}(a, b)$, $a > 0$, $b > 0$ independently of $\sigma_1, \sigma_2, \ldots$

$\sigma_j = \tau_1 + \cdots + \tau_j$, $j \geq 1$ with $\tau_1, \tau_2, \ldots \overset{i.i.d.}{\sim} \mathcal{E}(q)$, $q > 0$

k is a zero mean normal density on $\mathbb{R}$ with standard deviation q^{-1}

and finally $K(y) = \int_{-\infty}^{y} k(x)dx$, $y \in \mathbb{R}$.

See also Dykstra & Laud (1981), Lo & Weng (1989) and James (2003).

The treatment/placebo scenario

It is a simple important case of the proportional hazards model, in which

$$x_i \in \{0, 1\}$$

for all $i = 1 \ldots N$. The main goal is determining whether the hazard ratio

$$\zeta = e^{\beta}$$

is significantly different from one. In this case, the conjugate choice

$$\rho_\star \perp\!\!\!\perp \zeta \sim \mathcal{G}(c, d)$$

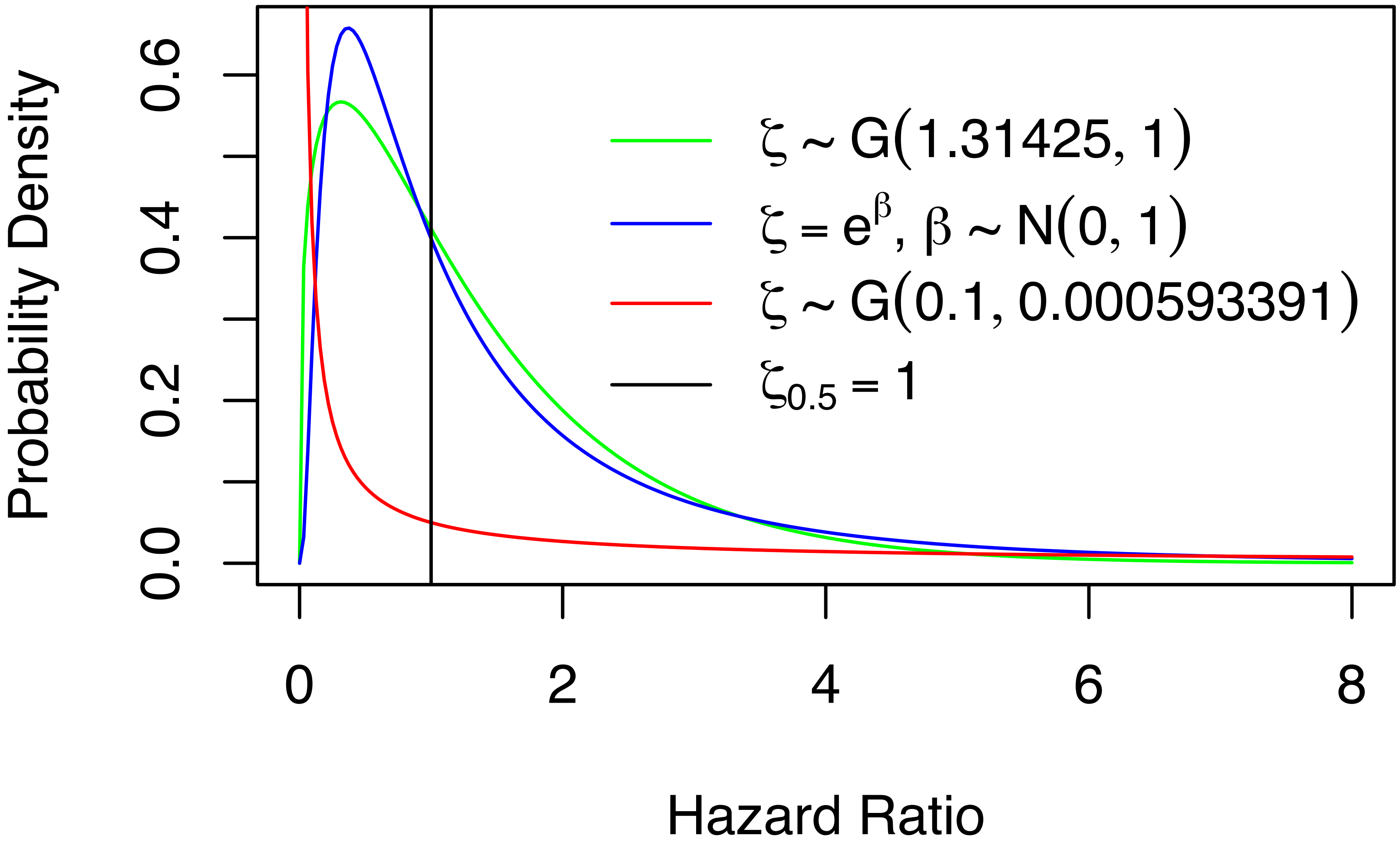
is possible, which helps the implementation of a Gibbs-type MCMC solution.

When no specific prior information is available, condition

$$\mathbb{P}\{\zeta < 1\} = \mathbb{P}\{\zeta > 1\}$$

can be imposed in order to help fixing the values of c and d.

Prior Comparison Plot



The leukemia remission times

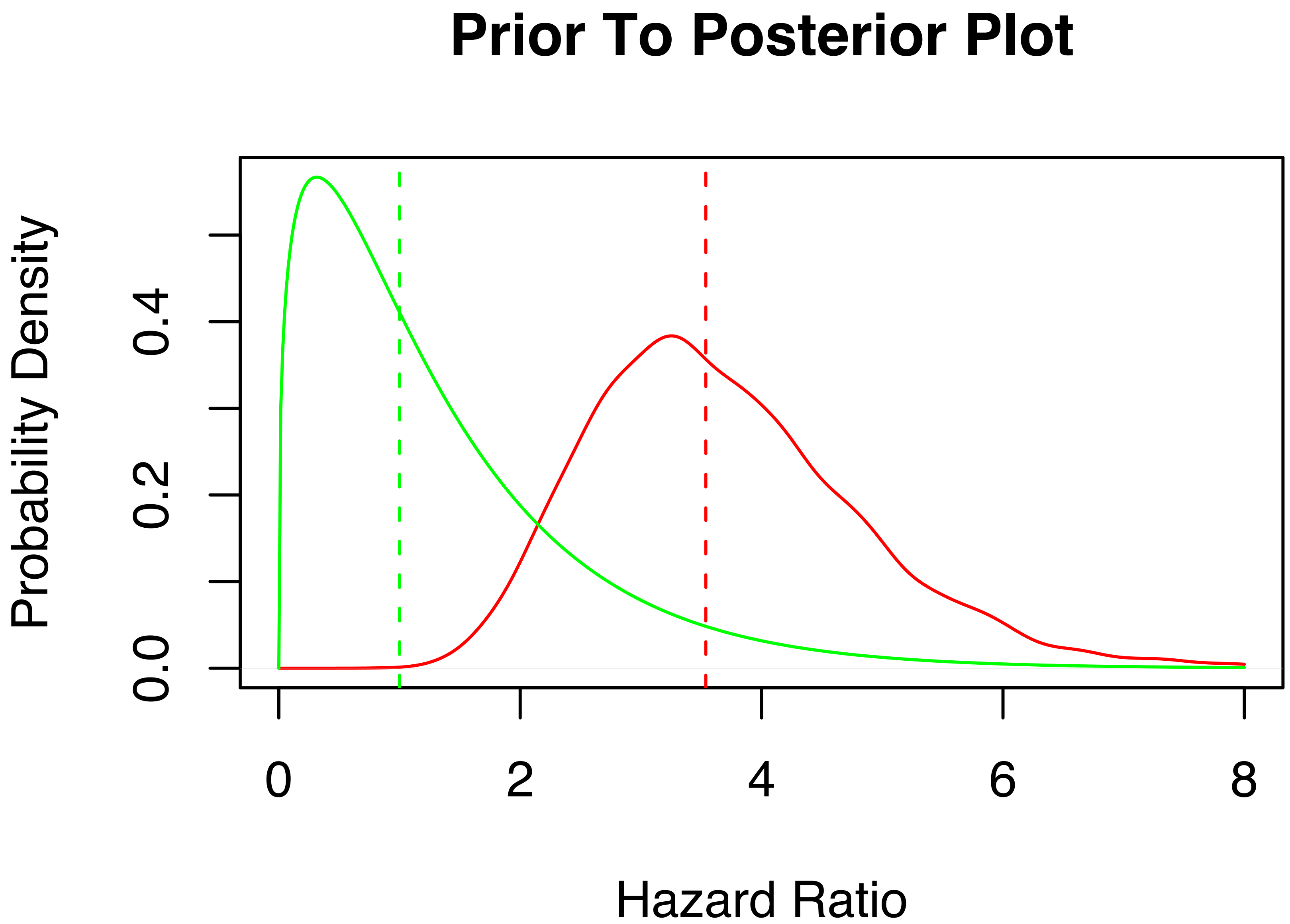
A well known dataset has been analyzed, in order to validate the suggested approach.

Data consist of 21 treatment/placebo pairs of leukemia remission times, with 12 right censored observations in the group of treated patients, clearly showing a shorter remission for patients receiving placebo.

The hyperparameters a, b and q have been chosen by setting

$$\begin{aligned} q t_{(n)} &= 10 \\ \mathbb{E}[\rho_\star(s)] &\equiv \frac{\sum_{i=1}^{n} \mathbb{I}_{\{o_i=1, x_i=0\}}}{\sum_{i=1}^{n} t_i \mathbb{I}_{\{x_i=0\}}}, \qquad s \in \mathbb{R}_+ \\ \frac{\mathbb{S}\mathrm{td}[\rho_\star(s)]}{\mathbb{E}[\rho_\star(s)]} &\to 1, \quad \text{as } s \to \infty \end{aligned}$$

and an *ad hoc* MCMC solution has been implemented in R.


Prior To Posterior Plot
Probability Density
0.0
0.2
0.4
0
2
4
6
8
Hazard Ratio

Estimation of the regression coefficient

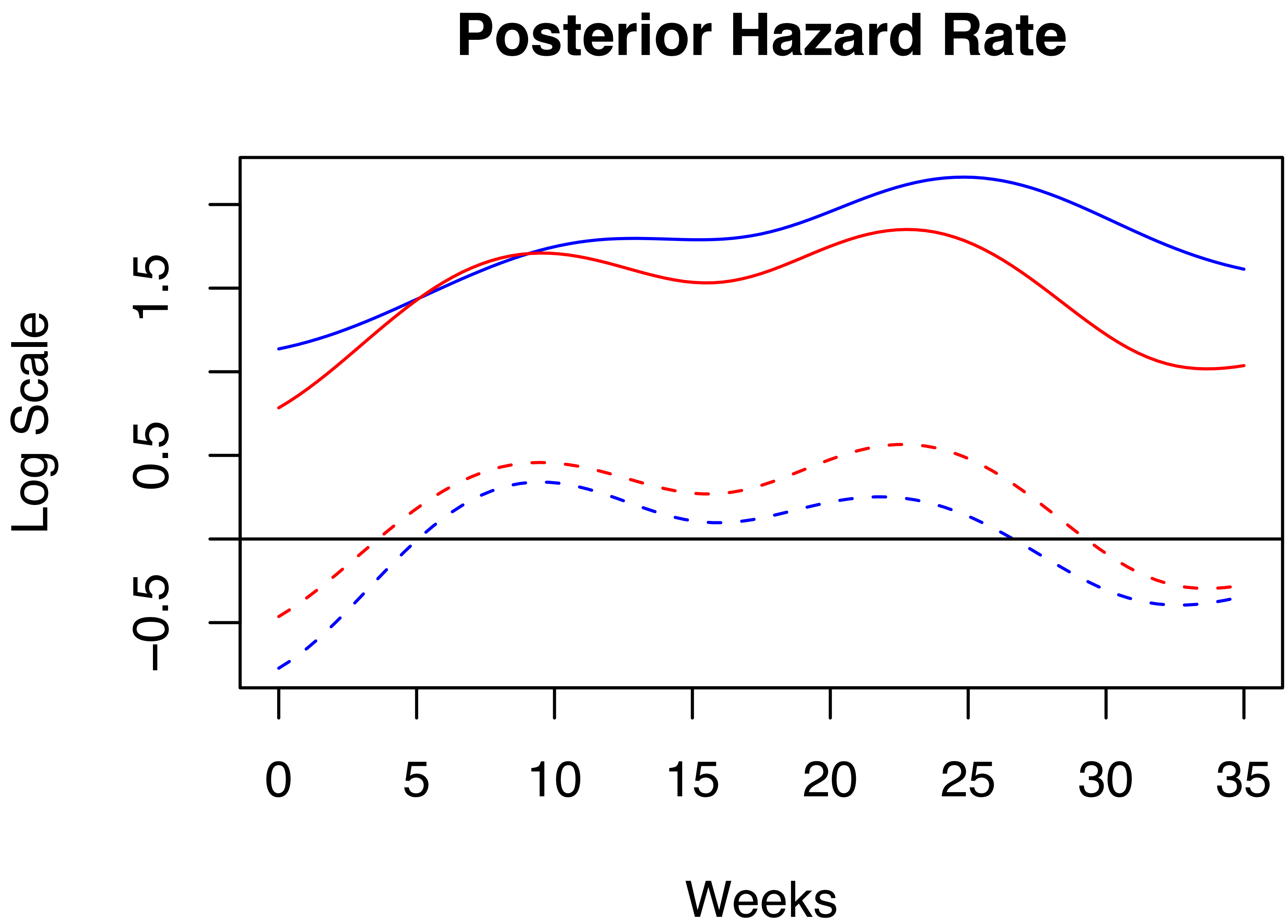
The posterior expected value of β is found to be

$$\widehat{\beta} = 1.26$$

which compared with the available estimates

	$\widehat{\beta}$
Cox (1972)	1.65
Kalbfleish (1978)	1.46–1.61
Laud *et al.* (1998)	1.62–1.71
Ibrahim *et al.* (2001)	1.59

clearly shows that the suggested approach is conservative.


Posterior Hazard Rate
Log Scale
1.5
0.5
−0.5
0
5
10
15
20
25
30
35
Weeks