

Parametric proportional hazards and accelerated failure time models

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Abstract

A unified implementation of parametric proportional hazards (PH) and accelerated failure time (AFT) models for right-censored or interval-censored and left-truncated data is described. The description here is valid for time-constant covariates, but the necessary modifications for handling time-varying covariates are implemented in `eha`. Note that only piecewise constant time variation is handled.

1 Introduction

There is a need for software for analyzing parametric proportional hazards (PH) and accelerated failure time (AFT) data, that are right or interval censored and left truncated.

2 The proportional hazards model

We define proportional hazards models in terms of an expansion of a given survivor function S_0 ,

$$s_{\boldsymbol{\theta}}(t; \mathbf{z}) = \{S_0(g(t, \boldsymbol{\theta}))\}^{\exp(\mathbf{z}\boldsymbol{\beta})}, \quad (1)$$

where $\boldsymbol{\theta}$ is a parameter vector used in modeling the baseline distribution, $\boldsymbol{\beta}$ is the vector of regression parameters, and g is a positive function, which helps defining a parametric family of baseline survivor functions through

$$S(t; \boldsymbol{\theta}) = S_0(g(t, \boldsymbol{\theta})), \quad t > 0, \quad \boldsymbol{\theta} \in \boldsymbol{\Theta}. \quad (2)$$

With f_0 and h_0 defined as the density and hazard functions corresponding to S_0 , respectively, the density function corresponding to S is

$$\begin{aligned} f(t; \boldsymbol{\theta}) &= -\frac{\partial}{\partial t} S(t, \boldsymbol{\theta}) \\ &= -\frac{\partial}{\partial t} S_0(g(t, \boldsymbol{\theta})) \\ &= g_t(t, \boldsymbol{\theta}) f_0(g(t, \boldsymbol{\theta})), \end{aligned}$$

where

$$g_t(t, \boldsymbol{\theta}) = \frac{\partial}{\partial t} g(t, \boldsymbol{\theta}).$$

Correspondingly, the hazard function is

$$\begin{aligned} h(t; \boldsymbol{\theta}) &= \frac{f(t; \boldsymbol{\theta})}{S(t; \boldsymbol{\theta})} \\ &= g_t(t, \boldsymbol{\theta}) h_0(g(t, \boldsymbol{\theta})). \end{aligned} \tag{3}$$

So, the proportional hazards model is

$$\begin{aligned} \lambda_{\boldsymbol{\theta}}(t; \mathbf{z}) &= h(t; \boldsymbol{\theta}) \exp(\mathbf{z}\boldsymbol{\beta}) \\ &= g_t(t, \boldsymbol{\theta}) h_0(g(t, \boldsymbol{\theta})) \exp(\mathbf{z}\boldsymbol{\beta}), \end{aligned} \tag{4}$$

corresponding to (1).

2.1 Data and the likelihood function

Given left truncated and right or interval censored data $(s_i, t_i, u_i, d_i, \mathbf{z}_i)$, $i = 1, \dots, n$ and the model (4), the likelihood function becomes

$$\begin{aligned} L((\boldsymbol{\theta}, \boldsymbol{\beta}); (\mathbf{s}, \mathbf{t}, \mathbf{u}, \mathbf{d}), \mathbf{Z}) &= \prod_{i=1}^n \{ (h(t_i; \boldsymbol{\theta}) \exp(\mathbf{z}_i \boldsymbol{\beta}))^{I_{\{d_i=1\}}} \\ &\quad \times (S(t_i; \boldsymbol{\theta})^{\exp(\mathbf{z}_i \boldsymbol{\beta})})^{I_{\{d_i \neq 2\}}} \\ &\quad \times (S(t_i; \boldsymbol{\theta})^{\exp(\mathbf{z}_i \boldsymbol{\beta})} - S(u_i; \boldsymbol{\theta})^{\exp(\mathbf{z}_i \boldsymbol{\beta})})^{I_{\{d_i=2\}}} \\ &\quad \times S(s_i; \boldsymbol{\theta})^{-\exp(\mathbf{z}_i \boldsymbol{\beta})} \} \end{aligned} \tag{5}$$

Here, for $i = 1, \dots, n$, $s_i < t_i \leq u_i$ are the left truncation and exit intervals, respectively, $d_i = 0$ means that $t_i = u_i$ and right censoring at u_i , $d_i = 1$ means that $t_i = u_i$ and an event at u_i , and $d_i = 2$ means that $t_i < u_i$ and an event occurs in the interval (t_i, u_i) (interval censoring) and $\mathbf{z}_i = (z_{i1}, \dots, z_{ip})$ is a vector of explanatory variables with corresponding parameter vector $\boldsymbol{\beta} = (\beta_1, \dots, \beta_p)$, $i = 1, \dots, n$.

From (5) we now get the log likelihood and the score vector in a straightforward manner.

$$\begin{aligned}
\ell((\boldsymbol{\theta}, \boldsymbol{\beta}); (\mathbf{s}, \mathbf{t}, \mathbf{u}, \mathbf{d}), \mathbf{Z}) &= \sum_{i:d_i=1} \{\log h(t_i; \boldsymbol{\theta}) + \mathbf{z}_i \boldsymbol{\beta}\} \\
&+ \sum_{i:d_i \neq 2} e^{\mathbf{z}_i \boldsymbol{\beta}} \log S(u_i; \boldsymbol{\theta}) \\
&+ \sum_{i:d_i=2} \log \{S(t_i; \boldsymbol{\theta})^{e^{\mathbf{z}_i \boldsymbol{\beta}}} - S(u_i; \boldsymbol{\theta})^{e^{\mathbf{z}_i \boldsymbol{\beta}}}\} \\
&- \sum_{i=1}^n e^{\mathbf{z}_i \boldsymbol{\beta}} \log S(s_i; \boldsymbol{\theta})
\end{aligned} \tag{6}$$

and (in the following we drop the long argument list to ℓ), for the regression parameters $\boldsymbol{\beta}$,

$$\begin{aligned}
\frac{\partial}{\partial \beta_j} \ell &= \sum_{i:d_i=1} z_{ij} \\
&+ \sum_{i:d_i \neq 2} z_{ij} e^{\mathbf{z}_i \boldsymbol{\beta}} \log S(t_i; \boldsymbol{\theta}) \\
&+ \sum_{i:d_i=2} z_{ij} e^{\mathbf{z}_i \boldsymbol{\beta}} \frac{S(t_i; \boldsymbol{\theta})^{e^{\mathbf{z}_i \boldsymbol{\beta}}} \log S(t_i; \boldsymbol{\theta}) - S(u_i; \boldsymbol{\theta})^{e^{\mathbf{z}_i \boldsymbol{\beta}}} \log S(u_i; \boldsymbol{\theta})}{S(t_i; \boldsymbol{\theta})^{e^{\mathbf{z}_i \boldsymbol{\beta}}} - S(u_i; \boldsymbol{\theta})^{e^{\mathbf{z}_i \boldsymbol{\beta}}}} \\
&- \sum_{i=1}^n z_{ij} e^{\mathbf{z}_i \boldsymbol{\beta}} \log S(s_i; \boldsymbol{\theta}), \quad j = 1, \dots, p,
\end{aligned} \tag{7}$$

and for the “baseline” parameters $\boldsymbol{\theta}$, in vector form,

$$\begin{aligned}
\frac{\partial}{\partial \boldsymbol{\theta}} \ell &= \sum_{i:d_i=1} \frac{h_{\boldsymbol{\theta}}(t_i; \boldsymbol{\theta})}{h(t_i; \boldsymbol{\theta})} \\
&+ \sum_{i:d_i \neq 2} e^{\mathbf{z}_i \boldsymbol{\beta}} \frac{S_{\boldsymbol{\theta}}(t_i; \boldsymbol{\theta})}{S(t_i; \boldsymbol{\theta})} \\
&+ \sum_{i:d_i=2} e^{\mathbf{z}_i \boldsymbol{\beta}} \frac{S(t_i; \boldsymbol{\theta})^{e^{\mathbf{z}_i \boldsymbol{\beta}}-1} S_{\boldsymbol{\theta}}(t_i; \boldsymbol{\theta}) - S(u_i; \boldsymbol{\theta})^{e^{\mathbf{z}_i \boldsymbol{\beta}}-1} S_{\boldsymbol{\theta}}(u_i; \boldsymbol{\theta})}{S(t_i; \boldsymbol{\theta})^{e^{\mathbf{z}_i \boldsymbol{\beta}}} - S(u_i; \boldsymbol{\theta})^{e^{\mathbf{z}_i \boldsymbol{\beta}}}} \\
&- \sum_{i=1}^n e^{\mathbf{z}_i \boldsymbol{\beta}} \frac{S_{\boldsymbol{\theta}}(s_i; \boldsymbol{\theta})}{S(s_i; \boldsymbol{\theta})}.
\end{aligned} \tag{8}$$

From (3),

$$\begin{aligned}
h_{\boldsymbol{\theta}}(t, \boldsymbol{\theta}) &= \frac{\partial}{\partial \boldsymbol{\theta}} h(t, \boldsymbol{\theta}) \\
&= g_{t\boldsymbol{\theta}}(t, \boldsymbol{\theta}) h_0(g(t, \boldsymbol{\theta})) + g_t(t, \boldsymbol{\theta}) g_{\boldsymbol{\theta}}(t, \boldsymbol{\theta}) h'_0(g(t, \boldsymbol{\theta})),
\end{aligned} \tag{9}$$

and, from (2),

$$\begin{aligned} S_{\boldsymbol{\theta}}(t; \boldsymbol{\theta}) &= \frac{\partial}{\partial \boldsymbol{\theta}} S(t; \boldsymbol{\theta}) = \frac{\partial}{\partial \boldsymbol{\theta}} S_0(g(t, \boldsymbol{\theta})) \\ &= -g_{\boldsymbol{\theta}}(t, \boldsymbol{\theta}) f_0(g(t, \boldsymbol{\theta})). \end{aligned} \quad (10)$$

For estimating standard errors, the observed information (the negative of the hessian) is useful. However, instead of the error-prone and tedious work of calculating analytic second-order derivatives, we will rely on approximations by numerical differentiation.

3 The shape–scale families

From (1) we get a *shape–scale* family of distributions by choosing $\boldsymbol{\theta} = (p, \lambda)$ and

$$g(t, (p, \lambda)) = \left(\frac{t}{\lambda}\right)^p, \quad t \geq 0; \quad p, \lambda > 0.$$

However, for reasons of efficient numerical optimization and normality of parameter estimates, we use the parametrisation $p = \exp(\gamma)$ and $\lambda = \exp(\alpha)$, thus redefining g to

$$g(t, (\gamma, \alpha)) = \left(\frac{t}{\exp(\alpha)}\right)^{\exp(\gamma)}, \quad t \geq 0; \quad -\infty < \gamma, \alpha < \infty. \quad (11)$$

For the calculation of the score and hessian of the log likelihood function, we need some partial derivatives of g . They are found in an appendix.

3.1 The Weibull family of distributions

The Weibull family of distributions is obtained by

$$S_0(t) = \exp(-t), \quad t \geq 0,$$

leading to

$$f_0(t) = \exp(-t), \quad t \geq 0,$$

and

$$h_0(t) = 1, \quad t \geq 0.$$

We need some first and second order derivatives of f and h , and they are particularly simple in this case, for h they are both zero, and for f we get

$$f'_0(t) = -\exp(-t), \quad t \geq 0.$$

3.2 The EV family of distributions

The EV (Extreme Value) family of distributions is obtained by setting

$$h_0(t) = \exp(t), \quad t \geq 0,$$

leading to

$$S_0(t) = \exp\{-(\exp(t) - 1)\}, \quad t \geq 0,$$

The rest of the necessary functions are easily derived from this.

3.3 The Gompertz family of distributions

The Gompertz family of distributions is given by

$$h(t) = \tau \exp(t/\lambda), \quad t \geq 0; \quad \tau, \lambda > 0.$$

This family is not directly possible to generate from the described shape-scale models, so it is treated separately by direct maximum likelihood.

3.4 Other families of distributions

Included in the *eha* package are the lognormal and the loglogistic distributions as well.

4 The accelerated failure time model

In the description of this family of models, we generate a shape-scale family of distributions as defined by the equations (2) and (11). We get

$$\begin{aligned} S(t; (\gamma, \alpha)) &= S_0(g(t, (\gamma, \alpha))) \\ &= S_0\left(\left\{\frac{t}{\exp(\alpha)}\right\}^{\exp(\gamma)}\right), \quad t > 0, \quad -\infty < \gamma, \alpha < \infty. \end{aligned} \quad (12)$$

Given a vector $\mathbf{z} = (z_1, \dots, z_p)$ of explanatory variables and a vector of corresponding regression coefficients $\boldsymbol{\beta} = (\beta_1, \dots, \beta_p)$, the AFT regression model is defined by

$$\begin{aligned} S(t; (\gamma, \alpha, \boldsymbol{\beta})) &= S_0(g(t \exp(\mathbf{z}\boldsymbol{\beta}), (\gamma, \alpha))) \\ &= S_0\left(\left\{\frac{t \exp(\mathbf{z}\boldsymbol{\beta})}{\exp(\alpha)}\right\}^{\exp(\gamma)}\right) \\ &= S_0\left(\left\{\frac{t}{\exp(\alpha - \mathbf{z}\boldsymbol{\beta})}\right\}^{\exp(\gamma)}\right) \\ &= S_0(g(t, (\gamma, \alpha - \mathbf{z}\boldsymbol{\beta}))), \quad t > 0. \end{aligned} \quad (13)$$

So, by defining $\boldsymbol{\theta} = (\gamma, \alpha - \mathbf{z}\boldsymbol{\beta})$, we are back in the framework of Section 2. We get

$$f(t; \boldsymbol{\theta}) = g_t(t, \boldsymbol{\theta}) f_0(g(t, \boldsymbol{\theta}))$$

and

$$h(t; \boldsymbol{\theta}) = g_t(t, \boldsymbol{\theta}) h_0(g(t, \boldsymbol{\theta})), \quad (14)$$

defining the AFT model generated by the survivor function S_0 and corresponding density f_0 and hazard h_0 .

4.1 Data and the likelihood function

Given left truncated and right or interval censored data $(s_i, t_i, u_i, d_i, \mathbf{z}_i)$, $i = 1, \dots, n$ and the model (14), the likelihood function becomes

$$\begin{aligned} L((\gamma, \alpha, \boldsymbol{\beta}); (\mathbf{s}, \mathbf{t}, \mathbf{d}), \mathbf{Z}) &= \prod_{i=1}^n \{ h(t_i; \boldsymbol{\theta}_i)^{I_{\{d_i=1\}}} \\ &\quad \times S(t_i; \boldsymbol{\theta}_i)^{I_{\{i \neq 2\}}} \\ &\quad \times (S(t_i; \boldsymbol{\theta}_i) - S(u_i; \boldsymbol{\theta}_i))^{I_{\{d_i=2\}}} \\ &\quad \times S(s_i; \boldsymbol{\theta}_i)^{-1} \} \end{aligned} \quad (15)$$

Here, for $i = 1, \dots, n$, $s_i < t_i \leq u_i$ are the left truncation and exit intervals, respectively, $d_i = 0$ means that $t_i = u_i$ and right censoring at t_i , $d_i = 1$ means that $t_i = u_i$ and an event at t_i , and $d_i = 2$ means that $t_i < u_i$ and an event occurs in the interval (t_i, u_i) (interval censoring), and $\mathbf{z}_i = (z_{i1}, \dots, z_{ip})$ is a vector of explanatory variables with corresponding parameter vector $\boldsymbol{\beta} = (\beta_1, \dots, \beta_p)$, $i = 1, \dots, n$.

From (15) we now get the log likelihood and the score vector in a straightforward manner.

$$\begin{aligned} \ell((\gamma, \alpha, \boldsymbol{\beta}); (\mathbf{s}, \mathbf{t}, \mathbf{u}, \mathbf{d}), \mathbf{Z}) &= \sum_{i: d_i=1} \log h(t_i; \boldsymbol{\theta}_i) \\ &\quad + \sum_{i: d_i \neq 2} \log S(t_i; \boldsymbol{\theta}_i) \\ &\quad + \sum_{i: d_i=2} \log (S(t_i; \boldsymbol{\theta}_i) - S(u_i; \boldsymbol{\theta}_i)) \\ &\quad - \sum_{i=1}^n \log S(s_i; \boldsymbol{\theta}_i) \end{aligned}$$

and (in the following we drop the long argument list to ℓ), for the regression parameters $\boldsymbol{\beta}$,

$$\begin{aligned}
\frac{\partial}{\partial \beta_j} \ell &= \sum_{d_i=1} \frac{h_j(t_i, \boldsymbol{\theta}_i)}{h(t_i, \boldsymbol{\theta}_i)} + \sum_{d_i \neq 2} \frac{S_j(t_i; \boldsymbol{\theta}_i)}{S(t_i; \boldsymbol{\theta}_i)} \\
&\quad + \sum_{d_i=2} \frac{S_j(t_i; \boldsymbol{\theta}_i) - S_j(u_i; \boldsymbol{\theta}_i)}{S(t_i; \boldsymbol{\theta}_i) - S(u_i; \boldsymbol{\theta}_i)} - \sum_{i=1}^n \frac{S_j(s_i; \boldsymbol{\theta}_i)}{S(s_i; \boldsymbol{\theta}_i)} \\
&= - \sum_{d_i=1} z_{ij} \frac{h_\alpha(t_i, \boldsymbol{\theta}_i)}{h(t_i, \boldsymbol{\theta}_i)} - \sum_{d_i \neq 2} z_{ij} \frac{S_\alpha(t_i; \boldsymbol{\theta}_i)}{S(t_i; \boldsymbol{\theta}_i)} \\
&\quad - \sum_{d_i=2} z_{ij} \frac{S_\alpha(t_i; \boldsymbol{\theta}_i) - S_\alpha(u_i; \boldsymbol{\theta}_i)}{S(t_i; \boldsymbol{\theta}_i) - S(u_i; \boldsymbol{\theta}_i)} + \sum_{i=1}^n z_{ij} \frac{S_\alpha(s_i; \boldsymbol{\theta}_i)}{S(s_i; \boldsymbol{\theta}_i)}
\end{aligned}$$

and for the “baseline” parameters γ and α ,

$$\begin{aligned}
\frac{\partial}{\partial \gamma} \ell &= \sum_{i:d_i=1} \frac{h_\gamma(t_i, \boldsymbol{\theta}_i)}{h(t_i, \boldsymbol{\theta}_i)} + \sum_{i:d_i \neq 2} \frac{S_\gamma(t_i; \boldsymbol{\theta}_i)}{S(t_i; \boldsymbol{\theta}_i)} \\
&\quad + \sum_{i:d_i=2} \frac{S_\gamma(t_i; \boldsymbol{\theta}_i) - S_\gamma(u_i; \boldsymbol{\theta}_i)}{S(t_i; \boldsymbol{\theta}_i) - S(u_i; \boldsymbol{\theta}_i)} - \sum_{i=1}^n \frac{S_\gamma(s_i; \boldsymbol{\theta}_i)}{S(s_i; \boldsymbol{\theta}_i)},
\end{aligned}$$

and

$$\begin{aligned}
\frac{\partial}{\partial \alpha} \ell &= \sum_{i:d_i=1} \frac{h_\alpha(t_i, \boldsymbol{\theta}_i)}{h(t_i, \boldsymbol{\theta}_i)} + \sum_{i:d_i \neq 2} \frac{S_\alpha(t_i; \boldsymbol{\theta}_i)}{S(t_i; \boldsymbol{\theta}_i)} \\
&\quad + \sum_{i:d_i=2} \frac{S_\alpha(t_i; \boldsymbol{\theta}_i) - S_\alpha(u_i; \boldsymbol{\theta}_i)}{S(t_i; \boldsymbol{\theta}_i) - S(u_i; \boldsymbol{\theta}_i)} - \sum_{i=1}^n \frac{S_\alpha(s_i; \boldsymbol{\theta}_i)}{S(s_i; \boldsymbol{\theta}_i)}.
\end{aligned}$$

Here, from (3),

$$\begin{aligned}
h_\gamma(t, \boldsymbol{\theta}_i) &= \frac{\partial}{\partial \gamma} h(t, \boldsymbol{\theta}_i) \\
&= g_{t\gamma}(t, \boldsymbol{\theta}_i) h_0(g(t, \boldsymbol{\theta}_i)) + g_t(t, \boldsymbol{\theta}_i) g_\gamma(t, \boldsymbol{\theta}_i) h'_0(g(t, \boldsymbol{\theta}_i)),
\end{aligned}$$

$$\begin{aligned}
h_\alpha(t, \boldsymbol{\theta}_i) &= \frac{\partial}{\partial \alpha} h(t, \boldsymbol{\theta}_i) \\
&= g_{t\alpha}(t, \boldsymbol{\theta}_i) h_0(g(t, \boldsymbol{\theta}_i)) + g_t(t, \boldsymbol{\theta}_i) g_\alpha(t, \boldsymbol{\theta}_i) h'_0(g(t, \boldsymbol{\theta}_i)),
\end{aligned}$$

and

$$\begin{aligned}
h_j(t, \boldsymbol{\theta}_i) &= \frac{\partial}{\partial \beta_j} h(t, \boldsymbol{\theta}_i) = \frac{\partial}{\partial \alpha} h(t, \boldsymbol{\theta}_i) \frac{\partial}{\partial \beta_j} (\alpha - \mathbf{z}_i \boldsymbol{\beta}) \\
&= -z_{ij} h_\alpha(t, \boldsymbol{\theta}_i), \quad j = 1, \dots, p.
\end{aligned}$$

Similarly, from (2) we get

$$\begin{aligned} S_\gamma(t; \boldsymbol{\theta}_i) &= \frac{\partial}{\partial \gamma} S(t; \boldsymbol{\theta}_i) = \frac{\partial}{\partial \gamma} S_0(g(t, \boldsymbol{\theta}_i)) \\ &= -g_\gamma(t, \boldsymbol{\theta}_i) f_0(g(t, \boldsymbol{\theta}_i)), \end{aligned}$$

$$\begin{aligned} S_\alpha(t; \boldsymbol{\theta}_i) &= \frac{\partial}{\partial \alpha} S(t; \boldsymbol{\theta}_i) = \frac{\partial}{\partial \alpha} S_0(g(t, \boldsymbol{\theta}_i)) \\ &= -g_\alpha(t, \boldsymbol{\theta}_i) f_0(g(t, \boldsymbol{\theta}_i)). \end{aligned}$$

and

$$\begin{aligned} S_j(t; \boldsymbol{\theta}_i) &= \frac{\partial}{\partial \beta_j} S(t; \boldsymbol{\theta}_i) = \frac{\partial}{\partial \alpha} S_0(g(t, \boldsymbol{\theta}_i)) \frac{\partial}{\partial \beta_j} (\alpha - \mathbf{z}_i \boldsymbol{\beta}) \\ &= -z_{ij} S_\alpha(t, \boldsymbol{\theta}_i), \quad j = 1, \dots, p. \end{aligned}$$

For estimating standard errors, the observed information (the negative of the hessian) is useful, so

$$\begin{aligned} -\frac{\partial^2}{\partial \beta_j \partial \beta_m} \ell &= -\sum_{i: d_i=1} z_{ij} z_{im} \left\{ \frac{h_{\alpha\alpha}(t_i, \boldsymbol{\theta}_i)}{h(t_i, \boldsymbol{\theta}_i)} - \left(\frac{h_\alpha(t_i, \boldsymbol{\theta}_i)}{h(t_i, \boldsymbol{\theta}_i)} \right)^2 \right\} \\ &\quad - \sum_{i: i \neq 2} z_{ij} z_{im} \left\{ \frac{S_{\alpha\alpha}(t_i, \boldsymbol{\theta}_i)}{S(t_i, \boldsymbol{\theta}_i)} - \left(\frac{S_\alpha(t_i, \boldsymbol{\theta}_i)}{S(t_i, \boldsymbol{\theta}_i)} \right)^2 \right\} \\ &\quad - \sum_{i: i=2} z_{ij} z_{im} \left\{ \frac{S_{\alpha\alpha}(t_i, \boldsymbol{\theta}_i) - S_{\alpha\alpha}(u_i, \boldsymbol{\theta}_i)}{S(t_i, \boldsymbol{\theta}_i) - S(u_i, \boldsymbol{\theta}_i)} - \left(\frac{S_\alpha(t_i, \boldsymbol{\theta}_i) - S_\alpha(u_i, \boldsymbol{\theta}_i)}{S(t_i, \boldsymbol{\theta}_i) - S(u_i, \boldsymbol{\theta}_i)} \right)^2 \right\} \\ &\quad + \sum_{i=1}^n z_{ij} z_{im} \left\{ \frac{S_{\alpha\alpha}(s_i, \boldsymbol{\theta}_i)}{S(s_i, \boldsymbol{\theta}_i)} - \left(\frac{S_\alpha(s_i, \boldsymbol{\theta}_i)}{S(s_i, \boldsymbol{\theta}_i)} \right)^2 \right\}, \quad j, m = 1, \dots, p, \end{aligned}$$

and

$$\begin{aligned}
-\frac{\partial^2}{\partial \beta_j \partial \tau} \ell &= \sum_{i:d_i=1} z_{ij} \left\{ \frac{h_{\alpha\tau}(t_i, \boldsymbol{\theta}_i)}{h(t_i, \boldsymbol{\theta}_i)} - \frac{h_{\alpha}(t_i, \boldsymbol{\theta}_i) h_{\tau}(t_i, \boldsymbol{\theta}_i)}{h^2(t_i, \boldsymbol{\theta}_i)} \right\} \\
&\quad + \sum_{i:i \neq 2} z_{ij} \left\{ \frac{S_{\alpha\tau}(t_i, \boldsymbol{\theta}_i)}{S(t_i, \boldsymbol{\theta}_i)} - \frac{S_{\alpha}(t_i, \boldsymbol{\theta}_i) S_{\tau}(t_i, \boldsymbol{\theta}_i)}{S^2(t_i, \boldsymbol{\theta}_i)} \right\} \\
&\quad + \sum_{i:i=2} z_{ij} \left\{ \frac{S_{\alpha\tau}(t_i, \boldsymbol{\theta}_i) - S_{\alpha\tau}(u_i, \boldsymbol{\theta}_i)}{S(t_i, \boldsymbol{\theta}_i) - S(u_i, \boldsymbol{\theta}_i)} \right. \\
&\quad \left. - \frac{(S_{\alpha}(t_i, \boldsymbol{\theta}_i) - S_{\alpha}(u_i, \boldsymbol{\theta}_i))(S_{\tau}(t_i, \boldsymbol{\theta}_i) - S_{\tau}(u_i, \boldsymbol{\theta}_i))}{(S(t_i, \boldsymbol{\theta}_i) - S(u_i, \boldsymbol{\theta}_i))^2} \right\} \\
&\quad - \sum_{i=1}^n z_{ij} \left\{ \frac{S_{\alpha\tau}(s_i, \boldsymbol{\theta}_i)}{S(s_i, \boldsymbol{\theta}_i)} - \frac{S_{\alpha}(s_i, \boldsymbol{\theta}_i) S_{\tau}(s_i, \boldsymbol{\theta}_i)}{S^2(s_i, \boldsymbol{\theta}_i)} \right\} \\
&\quad j = 1, \dots, p; \quad \tau = \gamma, \alpha,
\end{aligned}$$

and finally

$$\begin{aligned}
-\frac{\partial^2}{\partial \tau \partial \tau'} \ell &= - \sum_{i:d_i=1} \left\{ \frac{h_{\tau'\tau}(t_i, \boldsymbol{\theta}_i)}{h(t_i, \boldsymbol{\theta}_i)} - \frac{h_{\tau'}(t_i, \boldsymbol{\theta}_i) h_{\tau}(t_i, \boldsymbol{\theta}_i)}{h^2(t_i, \boldsymbol{\theta}_i)} \right\} \\
&\quad - \sum_{i:i \neq 2} \left\{ \frac{S_{\tau'\tau}(t_i, \boldsymbol{\theta}_i)}{S(t_i, \boldsymbol{\theta}_i)} - \frac{S_{\tau'}(t_i, \boldsymbol{\theta}_i) S_{\tau}(t_i, \boldsymbol{\theta}_i)}{S^2(t_i, \boldsymbol{\theta}_i)} \right\} \\
&\quad - \sum_{i:i=2} \left\{ \frac{S_{\tau'\tau}(t_i, \boldsymbol{\theta}_i) - S_{\tau'\tau}(u_i, \boldsymbol{\theta}_i)}{S(t_i, \boldsymbol{\theta}_i) - S(u_i, \boldsymbol{\theta}_i)} \right. \\
&\quad \left. - \frac{(S_{\tau'}(t_i, \boldsymbol{\theta}_i) - S_{\tau'}(u_i, \boldsymbol{\theta}_i))(S_{\tau}(t_i, \boldsymbol{\theta}_i) - S_{\tau}(u_i, \boldsymbol{\theta}_i))}{(S(t_i, \boldsymbol{\theta}_i) - S(u_i, \boldsymbol{\theta}_i))^2} \right\} \\
&\quad + \sum_{i=1}^n \left\{ \frac{S_{\tau'\tau}(s_i, \boldsymbol{\theta}_i)}{S(s_i, \boldsymbol{\theta}_i)} - \frac{S_{\tau'}(s_i, \boldsymbol{\theta}_i) S_{\tau}(s_i, \boldsymbol{\theta}_i)}{S^2(s_i, \boldsymbol{\theta}_i)} \right\} \\
&\quad (\tau, \tau') = (\gamma, \gamma), (\gamma, \alpha), (\alpha, \alpha).
\end{aligned}$$

The second order partial derivatives $h_{\tau\tau'}$ and $S_{\tau\tau'}$ are

$$\begin{aligned}
h_{\tau\tau'}(t, \boldsymbol{\theta}) &= \frac{\partial}{\partial \tau'} h_{\tau}(t, \boldsymbol{\theta}) \\
&= g_{t\tau\tau'}(t, \boldsymbol{\theta}) h_0(g(t, \boldsymbol{\theta})) + g_{t\tau}(t, \boldsymbol{\theta}) g_{\tau'}(t, \boldsymbol{\theta}) h_0'(g(t, \boldsymbol{\theta})) \\
&\quad + g_t(t, \boldsymbol{\theta}) g_{\theta}(t, \boldsymbol{\theta}) g_{\tau'}(t, \boldsymbol{\theta}) h_0''(g(t, \boldsymbol{\theta})) \\
&\quad + g_t(t, \boldsymbol{\theta}) g_{\theta\theta'}(t, \boldsymbol{\theta}) h_0'(g(t, \boldsymbol{\theta})) \\
&\quad + g_{t\tau'}(t, \boldsymbol{\theta}) g_{\theta}(t, \boldsymbol{\theta}) h_0'(g(t, \boldsymbol{\theta})) \\
&= h_0(g(t, \boldsymbol{\theta})) g_{t\tau\tau'}(t, \boldsymbol{\theta}) \\
&\quad + h_0'(g(t, \boldsymbol{\theta})) \{ g_t(t, \boldsymbol{\theta}) g_{\theta\theta'}(t, \boldsymbol{\theta}) \\
&\quad \quad + g_{t\tau}(t, \boldsymbol{\theta}) g_{\tau'}(t, \boldsymbol{\theta}) \\
&\quad \quad + g_{t\tau'}(t, \boldsymbol{\theta}) g_{\tau}(t, \boldsymbol{\theta}) \} \\
&\quad + h_0''(g(t, \boldsymbol{\theta})) g_t(t, \boldsymbol{\theta}) g_{\theta}(t, \boldsymbol{\theta}) g_{\tau'}(t, \boldsymbol{\theta}), \\
(\tau, \tau') &= (\gamma, \gamma), (\gamma, \lambda), (\lambda, \lambda),
\end{aligned} \tag{16}$$

and from (10),

$$\begin{aligned}
S_{\tau\tau'}(t, \boldsymbol{\theta}) &= \frac{\partial}{\partial \tau'} S_{\tau}(t, \boldsymbol{\theta}) \\
&= -\{ g_{\tau\tau'}(t, \boldsymbol{\theta}) f_0(g(t, \boldsymbol{\theta})) + g_{\tau}(t, \boldsymbol{\theta}) g_{\tau'}(t, \boldsymbol{\theta}) f_0'(g(t, \boldsymbol{\theta})) \}, \\
(\tau, \tau') &= (\gamma, \gamma), (\gamma, \lambda), (\lambda, \lambda).
\end{aligned} \tag{17}$$

A Some partial derivatives

The function (see (11))

$$g(t, (\gamma, \alpha)) = \left(\frac{t}{\exp(\alpha)} \right)^{\exp(\gamma)}, \quad t \geq 0; \quad -\infty < \gamma, \alpha < \infty. \tag{18}$$

has the following partial derivatives:

$$\begin{aligned}
g_t(t, (\gamma, \alpha)) &= \frac{\exp(\gamma)}{t} g(t, (\gamma, \alpha)), \quad t > 0 \\
g_{\gamma}(t, (\gamma, \alpha)) &= g(t, (\gamma, \alpha)) \log\{g(t, (\gamma, \alpha))\} \\
g_{\alpha}(t, (\gamma, \alpha)) &= -\exp(\gamma) g(t, (\gamma, \alpha))
\end{aligned}$$

$$\begin{aligned}
g_{t\gamma}(t, (\gamma, \alpha)) &= g_t(t, (\gamma, \alpha)) + \frac{\exp(\gamma)}{t} g_\gamma(t, (\gamma, \alpha)), \quad t > 0 \\
g_{t\alpha}(t, (\gamma, \alpha)) &= -\exp(\gamma) g_t(t, (\gamma, \alpha)), \quad t > 0 \\
g_{\gamma^2}(t, (\gamma, \alpha)) &= g_\gamma(t, (\gamma, \alpha)) \{1 + \log g(t, (\gamma, \alpha))\} \\
g_{\gamma\alpha}(t, (\gamma, \alpha)) &= g_\alpha(t, (\gamma, \alpha)) \{1 + \log g(t, (\gamma, \alpha))\} \\
g_{\alpha^2}(t, (\gamma, \alpha)) &= -\exp(\gamma) g_\alpha(t, (\gamma, \alpha))
\end{aligned}$$

$$\begin{aligned}
g_{t\gamma^2}(t, (\gamma, \alpha)) &= g_{t\gamma}(t, (\gamma, \alpha)) \\
&\quad + \frac{\exp(\gamma)}{t} g_\gamma(t, (\gamma, \alpha)) \{2 + \log g(t, (\gamma, \alpha))\} \\
g_{t\gamma\alpha}(t, (\gamma, \alpha)) &= -\exp(\gamma) \{g_t(t, (\gamma, \alpha)) + g_{t\gamma}(t, (\gamma, \alpha))\} \\
g_{t\alpha^2}(t, (\gamma, \alpha)) &= -\exp(\gamma) g_{t\alpha}(t, (\gamma, \alpha))
\end{aligned}$$

The formulas will be easier to read if we remove all function arguments, i.e., $(t, (\gamma, \alpha))$:

$$\begin{aligned}
g_t &= \frac{\exp(\gamma)}{t} g, \quad t > 0 \\
g_\gamma &= g \log g \\
g_\alpha &= -\exp(\gamma) g \\
g_{t\gamma} &= g_t + \frac{\exp(\gamma)}{t} g_\gamma, \quad t > 0 \\
g_{t\alpha} &= -\exp(\gamma) g_t, \quad t > 0 \\
g_{\gamma^2} &= g_\gamma \{1 + \log g\} \\
g_{\gamma\alpha} &= g_\alpha \{1 + \log g\} \\
g_{\alpha^2} &= -\exp(\gamma) g_\alpha \\
g_{t\gamma^2} &= g_{t\gamma} + \frac{\exp(\gamma)}{t} g_\gamma \{2 + \log g\}, \quad t > 0 \\
g_{t\gamma\alpha} &= -\exp(\gamma) \{g_t + g_{t\gamma}\}, \quad t > 0 \\
g_{t\alpha^2} &= -\exp(\gamma) g_{t\alpha}, \quad t > 0
\end{aligned}$$