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A Combined GEE/Buckley-James Method for Estimating an Accelerated Failure Time Model of Multivariate Failure Times

Ulrich Hornsteiner and Alfred Hamerle *

Abstract

The present paper deals with the estimation of a frailty model of multivariate failure times. The failure times are modeled by an Accelerated Failure Time Model including observed covariates and an unobservable frailty component. The frailty is assumed random and differs across elementary units, but is constant across the spells of a unit or a group. We develop an estimator (of the regression parameters) that combines the GEE approach (Liang and Zeger, 1986) with the Buckley-James estimator for censored data. This estimator is robust against violations of the correlation structure and the distributional assumptions. Some simulation studies are conducted in order to study the empirical performance of the estimator. Finally, the methods are applied to data of repeated appearances of malign ventricular arrhythmias at patients with implanted defibrillator.

Key words: Multivariate failure times; accelerated failure time model; generalized estimating equations; censored data; simulation study.

1 Introduction

Failure time data are collected in follow-up studies, retrospective studies, and sometimes in longitudinal panels. The data record qualitative changes over time in some important variables. The main purpose of the statistical analysis of such failure times is to investigate the time it takes before a certain event occurs. In addition, it is important to evaluate the association of exposure, treatment and prognostic factors with the distribution of time until the event occurs. The statistical theory of failure time data is described in standard textbooks including Kalbfleisch and Prentice (1980), Lawless (1982), Cox and Oakes (1984), Breslow and Day (1987), Blossfeld, Hamerle and Mayer (1989), Harris and Albert (1991), Collett (1994), or in a counting process framework for example Fleming and Harrington (1991) and Andersen et al. (1993).

Sometimes there is only one spell for each individual measuring the time interval between an initial event and a termination event. This applies in particular to survival analysis where the detection of a disease is the initial event and the patient's death is the termination event. However, the event of interest in clinical studies need not necessarily be death, but could, for example, be the end of a period spent in remission

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from a disease, relief from symptoms or the recurrence of a particular condition. In other areas such as economics, sociology, psychology or industrial engineering, study subjects can also experience more than one event or failure as time elapses and, moreover, these events or failures may be of various kinds.

Several researchers have studied models for multivariate failure times: Cox's proportional hazards regression model has been extended to the multivariate case e.g. by Prentice, Williams and Peterson (1981), Wei, Lin and Weissfeld (1989) and Prentice and Hsu (to appear). Prentice and Cai (1992) developed an estimator for bivariate survivor functions using the counting process theory. Linear models for multivariate failure times have been considered by Lin and Wei (1992), Lee, Wei and Ying (1993) and Murphy, Bentley and O'Hanesian (1995).

In the present paper two kinds of multivariate failure time data are considered. In the first case data arise from successive spells between recurrent events for the same study subject. Here the last spell of each unit is typically censored. Examples are successive unemployment spells, repeated purchases of a certain brand by a household, repeated appearances of malign ventricular arrhythmias at patients with implanted defibrillator, or the durations from one discharge to the next arrest of ex-prisoners who could not be reintegrated in society. In the second case we consider different but related elementary units (for example, two or more organs of one organism). For each unit a single spell is observed, and the spells within a cluster or block are dependent. Moreover, all spells may be censored.

We assume an Accelerated Failure Time Model where the logarithm of each failure time depends linearily on a vector of covariates. The most frequently used methods for estimating the model parameters begin by specifying the hazard function (corresponding to the specification of the error distribution in the linear model for $\ln T$ where T is the failure time) up to a finite set of parameters, after which the values of the regression coefficients and any further unknown parameters are estimated by maximum likelihood. Our approach is not to specify the error distribution of the linear model in $\ln T$ and thus the hazard function. Moreover, it is assumed that the dependence between the successive spells of an individual or the spells within a cluster can be modeled by an unobserved heterogeneity component that is person or cluster specific respectively. So the error term of the linear model consists of two additive components. We shall investigate in some detail an estimation method of the regression parameters that is robust against violations of the dependence structure and the distributional assumptions. For the construction of the estimator the GEE approach developed by Liang and Zeger (1986) for the analysis of longitudinal data is combined with the Buckley-James estimator to accommodate censored data. The performance of the proposed estimator is investigated in several simulation experiences. Finally, the method is applied to the defibrillator data.

2 The model

We consider an extension of an Accelerated Failure Time Model which is able to describe both the mentioned constellations of data. We have observed N groups or elementary units ($n = 1, \ldots, N$, henceforth: "blocks") and assume that the failure times are independent from block to block but are correlated within one block. The data consist of

K_n spells in the n^{th} block ($k = 1, \ldots, K_n$).

The logarithm of every failure time

$$y_{nk} = \ln(T_{nk}) = x'_{nk}\beta + \sigma_\alpha \alpha_n + \sigma_\varepsilon \varepsilon_{nk}$$

depends linearly on a vector x_{nk} of P covariates (including a 1 for the intercept) – which may partly be constant within the block and partly vary from member to member or from spell to spell – and a P-dimensional vector of regression parameters $\beta = (\beta_1, \ldots, \beta_P)'$, $p = 1, \ldots, P$ (Fahrmeir, Hamerle and Tutz, 1996, p. 310).

The stochastic component consists of a block effect α_n which absorbs non-observed block-constant covariates and an error term ε_{nk}. The α_n are assumed to be independently and identically distributed as $N(0, 1)$ (other distributions are also thinkable). The ε_{nk} can but need not be independent, their distribution is assumed to be one of the usual distributions in Accelerated Failure Time Models: The normal distribution leads to the Log-normal model, the logistic distribution to the Log-logistic model, and the extreme value distribution to the Weibull model. In the special case of independent ε_{nk} we have an equicorrelation structure with

$$Cov(y_{nk}, y_{ml}) = 0 \qquad \text{if} \quad n \neq m,$$

$$Cov(y_{nk}, y_{nl}) = \sigma_\alpha^2 \qquad \text{if} \quad k \neq l,$$

and

$$Var(y_{nk}) = \sigma_\alpha^2 + \sigma_\varepsilon^2 \qquad \forall n = 1, \ldots, N \;\; \forall k = 1, \ldots, K_n.$$

Instead of T_{nk} we observe

$$z_{nk} = \min(T_{nk}, c_{nk})$$

where c_{nk} is a censor value, together with an indicator variable

$$\delta_{nk} = \begin{cases} 1 & \text{if} \quad T_{nk} \leq c_{nk} \\ 0 & \text{if} \quad T_{nk} > c_{nk}. \end{cases}$$

We imagine various realizations of the censor value (Fahrmeir, Hamerle and Tutz, 1996, p. 303f): In the case of N groups the c_{nk} may be random variables which are independent of each other, of α_n, ε_{nk} and T_{nk} (random censoring) or can be an amount of time $c_{nk} \equiv c \; \forall n = 1, \ldots, N \;\; \forall k = 1, \ldots, K_n$ fixed before the beginning of the study (type I censoring). The effect that $c_{nk} \equiv c$ is the same if all the spells begin at the same time and the rate of units to be censored is fixed before the beginning of the study (type II censoring).

In the case of recurrent events of N units, however, it is usually the limited observation period C_n which is responsible for censoring. In this context we speak about type I censoring if $C_n \equiv C \;\; \forall n = 1, \ldots, N$ and about random censoring if C_n are random variables. In each of these cases we assume for simplicity that the beginning of the observation period coincides with an event, that yields

$$c_{nk} = C_n - \sum_{l=1}^{k-1} T_{nl} \quad \forall n = 1, \ldots, N \;\; \forall k = 1, \ldots, K_n.$$

Thus the last spell of each unit is censored almost surely.

3 The estimation method

3.1 The GEE part

Our aim was to develop an estimator of the regression parameters which is robust also if we can not be sure about the correlation structure and the distribution assumptions. In the *absence of censoring* the solution of the problem appears to be the GEE approach for longitudinal data (Liang and Zeger, 1986). The generalized estimating equations are

$$\sum_{n=1}^{N} X_n' V_n^{-1}(y_n - X_n\hat{\beta}) = 0,$$

where X_n is the matrix containing the lines x_{nk}', $k = 1, \ldots, K_n$, and $y_n = (y_{n1}, \ldots, y_{nK_n})'$. Furthermore $V_n = R_{K_n}(\gamma)/\phi$, where $R_{K_n}(\gamma)$ is a working correlation matrix, γ a vector that fully characterizes the correlation structure, and $1/\phi = Var(y_{nk}) := v$ is constant under suitable assumptions for α_n and ε_{nk}.

The iterative estimation procedure consists of a modified Fisher scoring for β and a moment estimation of γ and v. Given current estimates $\hat{\gamma}$ and $\hat{v}$ the iteration steps are

$$\hat{\beta}^{(u+1)} = \hat{\beta}^{(u)} + \left(\sum_{n=1}^{N} X_n' \tilde{V}_n^{-1}(\hat{\beta}^{(u)}) X_n\right)^{-1} \left(\sum_{n=1}^{N} X_n' \tilde{V}_n^{-1}(\hat{\beta}^{(u)}) \left(y_n - X_n\hat{\beta}^{(u)}\right)\right),$$

$u = 1, 2, \ldots$, where $\tilde{V}_n(\beta) = V_n(\hat{\gamma}(\beta, \hat{v}(\beta)))$.

Unlike Liang and Zeger (1986) we follow Spieß (1995), p. 32f, and Spieß and Hamerle (1995), p. 7, and estimate v by

$$\hat{v}(X, y, \beta) = \frac{1}{\sum_{n=1}^{N} K_n - P} \sum_{n=1}^{N} \sum_{k=1}^{K_n} \hat{r}_{nk}^2 - \left(\frac{1}{\sum_{n=1}^{N} K_n} \sum_{n=1}^{N} \sum_{k=1}^{K_n} \hat{r}_{nk}\right)^2,$$

where $r_{nk} = y_{nk} - x_{nk}'\beta$.

In general we consider three types of working correlation matrices. The equicorrelation type (equ) corresponds with independent ε_{nk} in the model. In this case $\gamma = Corr(y_{nk}, y_{nl})$, and $c := Cov(y_{nk}, y_{nl}) = v \cdot \gamma$ is estimated similar to v. The simplest type (ind) is calculated under the restriction $\gamma = 0$ which corresponds with $\sigma_\alpha = 0$ in the model. The third specification (ar1) is characterized by $Corr(y_{nk}, y_{nl}) = \rho^{|k-l|}$, $|\rho| < 1$ and $\gamma = \rho$ (for details about the calculation of $\hat{\rho}$ see Spieß, 1995, p. 33).

3.2 The Buckley-James part

However, in the case of censoring the y_{nk} are partially unknown. We solve this problem by replacing y_{nk} by

$$y_{nk}^* = \delta_{nk} \ln z_{nk} + (1 - \delta_{nk})\hat{E}(y_{nk} \mid y_{nk} > \ln z_{nk}).$$

This substitution is according to the iterative Least Squares method of Buckley and James (BJ, 1979) that was developed for estimating parameters in Accelerated Failure

Time Models where the residuals are independent but their distribution is unspecified. From this point of view, our method can be seen as a multivariate extension of the BJ procedure. For asymptotic properties of estimators of BJ type see e.g. Lai and Ying (1991).

In the absence of censoring the substitute equals y_{nk} but for censored data we estimate the conditional expectation of y_{nk} using the nonparametric product limit estimator (Kaplan and Meier, 1958).

3.3 The combined GEE/BJ method

As we have

$$Ey^*_{nk} = x'_{nk}\beta$$

in the next step we apply the GEE method to y^*_{nk}. In doing so we ignore some problems that appear in connection with the variance/covariance structure of the y^*_{nk} hoping that the robustness of the GEE estimator gets them under control.

Altogether, the estimation algorithm consists of at least three iteration steps. We get an initial estimation simply by $\hat{\beta}^{(0)} = (\tilde{X}'\tilde{X})^{-1}\tilde{X}'\tilde{y}$ where $\tilde{X}$ and $\tilde{y}$ solely include the uncensored spells. The first step of the u^{th} iteration ($u = 1, 2, \ldots$) is the BJ part in which $\hat{\beta}^{(u-1)}$ is used for computing the residuals and the (renewed) $y^{*(u)}_{nk}$. Both $\hat{\beta}^{(u-1)}$ and $y^{*(u)}_{nk}$ enter into the second step, the moment estimation $\hat{\gamma}^{(u)}$. All these are the basis for the third part, the Fisher scoring for $\hat{\beta}^{(u)}$.

We have to get along with the property of estimators of BJ type that they often do not converge but oscillate between two or even more points. Therefore, if after a given maximum number of iterations the convergence criteria are not fulfilled, the algorithm has to search for the loop in which the estimation procedure is trapped. The usual solution then is to take the averages of the relevant values as estimators (Miller, 1981, p. 152).

There is remaining one decisive point in the transfer from y_{nk} to y^*_{nk}. The derivation of the Fisher scoring step as well as the asymptotic covariance matrix use that $\frac{1}{N}\sum_{n=1}^{N}\frac{\partial}{\partial\beta}(y_n - x'_n\beta) \longrightarrow 0$ almost surely for $N \longrightarrow \infty$ (see Spieß, 1995, p. 66). Similar to Murphy, Bentley and O'Hanesian (1995), p. 1848, we have to consider that this is not valid for y^*_n so that

$$\hat{\beta}^{(u+1)} = \hat{\beta}^{(u)} + \left(\sum_{n=1}^{N} X'_n\tilde{V}_n^{-1}(\hat{\beta}^{(u)})\frac{\partial y^*_n}{\partial\beta}\right)^{-1}\left(\sum_{n=1}^{N} X'_n\tilde{V}_n^{-1}(\hat{\beta}^{(u)})\left(y^*_n - X'_n\hat{\beta}^{(u)}\right)\right),$$

$u = 1, 2, \ldots$, and an estimator of the asymptotic covariance matrix of the parameter estimations is

$$\widehat{Cov}(\hat{\beta}) = \left(\sum_{n=1}^{N} X'_n\tilde{V}_n^{-1}\frac{\partial y^*_n}{\partial\beta}\right)^{-1}\left(\sum_{n=1}^{N} X'_n\tilde{V}_n^{-1}\widehat{Cov}(y^*_n)\tilde{V}_n^{-1}X_n\right)\left(\sum_{n=1}^{N} X'_n\tilde{V}_n^{-1}\frac{\partial y^*_n}{\partial\beta}\right)^{-1},$$

where $\widehat{Cov}(y^*_n) = (y^*_n - x'_n\beta)\,(y^*_n - x'_n\beta)'$.

4 The simulation and estimation program

To study the properties of the developed estimator in finite samples under various conditions a simulation and estimation program was written in SAS/IML, version 6 (SAS Institute Inc., 1989, 1990).

In one running of the program S data sets are generated according to several input options. Mostly we work with $S = 200$ simulations. In every simulation, N blocks of covariates and failure times are produced. There are several options about the generation of the failure times and the censoring mechanism. One of them is the generation of **p**arallel **p**rocesses of K_n **r**elated elementary **u**nits (PPRU) in the n^{th} group, $n = 1, \ldots, N$. Another specification is the modeling of K_n **s**uccessive **s**pells separated by **r**ecurrent **e**vents (SSRE) of the n^{th} unit, $n = 1, \ldots, N$. In the latter case the total observation period C_n decides about the number of spells K_n and about the censoring of the last spell. For purposes of comparison we mention a third option which is similar to SSRE but does not generate censored data as each unit is observed until the last spell is completed (SSRE without censoring).

The design matrices consist of the column of ones and four stochastic regressors, two of them (x2 and x3) constant within one block, the second two (x4 and x5) varying from unit to unit or from spell to spell, respectively. In each of the two cases, one of the two is a metric, normally distributed variable having mean and variance one (x2 and x4), the other one is a dichotomous variable taking the two values zero and one with probability 0.5 each (x3 and x5). The regression coefficients $\beta_2, \ldots, \beta_5$ as well as the intercept β_1 are specified as 0.5 each.

Several assumptions about the distribution of α_n and ε_{nk} are possible: The independence case (ind) where $\alpha_n \equiv 0$, the equicorrelation case (equ) with the α_n being normally $N(0, \sigma_\alpha^2)$, loggamma or weibull distributed and the ε_{nk} – independent from each other – normally $N(0, \sigma_\varepsilon^2)$, logistic or extreme value distributed, the ar1 case with $\alpha_n \equiv 0$, and a combination of the latter two, the arh case.

Finally, the estimation part of the program requires convergence criteria, a maximum number of iterations, and the specification of the type of the working correlation matrix (ind, equ or ar1) as described in section 3.1.

The output contains the mean of the estimated parameter vectors,

$$\overline{\hat{\beta}} = \frac{1}{S} \sum_{s=1}^{S} \hat{\beta}_s,$$

and the root mean square error

$$RMSE(\hat{\beta}_p) = \left(\frac{1}{S-1} \sum_{s=1}^{S} \left(\hat{\beta}_{sp} - \beta_p \right)^2 \right)^{1/2}$$

and the standard deviation

$$s(\hat{\beta}_p) = \left(\frac{1}{S-1} \sum_{s=1}^{S} \left(\hat{\beta}_{sp} - \overline{\hat{\beta}}_p \right)^2 \right)^{1/2}$$

of each estimated parameter ($p = 1, \ldots, P$), estimated over the S simulations. The latter is used as quality criterion in comparison with the mean of the estimated standard deviations of $\hat{\beta}_p$,

$$\overline{\hat{\sigma}(\hat{\beta}_p)} = \frac{1}{S}\sum_{s=1}^{S}\left(\hat{\sigma}(\hat{\beta}_p)\right)_s$$

$(p = 1, \ldots, P)$, which we get as the roots of the diagonal elements of the covariance matrix estimation in section 3.3.

In addition to the numerical assessment of these values we apply statistical tests to control normality and bias of the parameter estimates. The SAS procedure PROC UNIVARIATE provides us with the p-values of the Shapiro-Wilk statistics testing each component of the estimated parameter vector if it is a random sample from a normal distribution. To test if a bias can be explained by the random character of the simulations or if it is significant, an F-test for the null hypothesis $E(\hat{\beta}) = \beta$ and t-tests for the null hypotheses $E(\hat{\beta}_p) = \beta_p$, $p = 1, \ldots, P$, are implemented in the IML program. Moreover, we yield statistics about convergence or oscillation of the iterations and about computation time.

5 Simulation results

The possibilities of varying the input options of the described simulation and estimation program are manifold. The most remarkable facts will be discussed in this section.

Firstly, it should be mentioned that there are no numerical or convergence problems with the GEE/BJ estimator as far as the censoring rate in the total data set does not exceed a value of about 60%. Indeed, with higher censoring rates we state an increasing occurrence of BJ-specific oscillations, and longer loops as well (see e.g. table 1), but it seems to be no problem to get them under control if we do not worry about the clearly increasing computation time.

The distributions of α_n and ε_{nk} seem to have no decisive influence on the results. For reasons of simplicity and comparable results in this paper we let $\alpha_n \overset{\text{iid}}{\sim} N(0,1)$ and $\varepsilon_{nk} \overset{\text{iid}}{\sim} N(0,1)$. Corresponding to this kind of data generation (and the most plausible correlation assumption within the scope of failure time analysis) we use the "equ" working correlation matrix in the estimation part, that means, we specify it correctly apart from some problems basing on the transformation from y to y^*. For a discussion on its misspecification see later in this section.

The first group of simulation results (table 1) intends to show some general properties of the estimation method especially in dependence of the censoring rate. We generated data of a medium sample size of $N = 200$ groups of $K_n \equiv 3$ related elementary units each (PPRU). The true structure was the equicorrelation structure with a moderate correlation of 0.5. The failure times were type II censored with various values of the censoring rate.

The differences of the means of the estimated parameters and the true parameters are small, not systematic and not significant. This result remained true for increasing censoring rates and was confirmed in all simulations of parallel processes of related elementary units. An effect is that the bias component of the root mean square errors is very small in relation to the variance component.

The parameter estimations are in nearly all cases compatible with the hypothesis that they are a sample of normal distributed variables (with one clear exception in

Table 1: $N = 200$ *groups of related elementary units of* $K_n \equiv 3$ *parallel processes each, data generation and estimation by equicorrelation structure,* $\sigma^2_\alpha = \sigma^2_\varepsilon = 0.05 \Rightarrow v = 0.10$, $c = 0.05$, *type II censoring with various censoring rates: Mean, RMSE and standard deviation of the regression estimations, mean of the estimated standard deviations, p-values and convergence statistics over* $S = 200$ *simulations*

censoring rate	0	1/6	2/6	3/6	4/6
$\overline{\hat\beta_1} = 0.$	4948	4943	4937	4931	4928
$\overline{\hat\beta_2} = 0.$	5018	5019	5025	5029	5030
$\overline{\hat\beta_3} = 0.$	5040	5042	5060	5055	5050
$\overline{\hat\beta_4} = 0.$	4998	4997	4994	4998	4993
$\overline{\hat\beta_5} = 0.$	5002	5012	5008	5016	5013
$RMSE(\hat\beta_1) = 0.$	0350	0374	0398	0416	0486
$RMSE(\hat\beta_2) = 0.$	0175	0189	0209	0245	0333
$RMSE(\hat\beta_3) = 0.$	0394	0421	0451	0469	0563
$RMSE(\hat\beta_4) = 0.$	0113	0136	0157	0192	0275
$RMSE(\hat\beta_5) = 0.$	0200	0216	0256	0304	0423
$s(\hat\beta_1) = 0.$	0347	0370	0393	0411	0481
$s(\hat\beta_2) = 0.$	0174	0188	0207	0243	0331
$s(\hat\beta_3) = 0.$	0392	0419	0447	0465	0561
$s(\hat\beta_4) = 0.$	0113	0136	0156	0192	0275
$s(\hat\beta_5) = 0.$	0200	0216	0256	0303	0423
$\overline{\hat\sigma(\hat\beta_1)} = 0.$	0348	0418	0438	0451	0482
$\overline{\hat\sigma(\hat\beta_2)} = 0.$	0182	0213	0228	0252	0301
$\overline{\hat\sigma(\hat\beta_3)} = 0.$	0364	0407	0456	0533	0673
$\overline{\hat\sigma(\hat\beta_4)} = 0.$	0105	0135	0158	0184	0230
$\overline{\hat\sigma(\hat\beta_5)} = 0.$	0211	0250	0298	0368	0494
p-values H_0: $\sim N$					
$\hat\beta_1$ (0. ....)	9902	9711	9428	9518	9025
$\hat\beta_2$ (0. ....)	6935	5461	4105	5555	4662
$\hat\beta_3$ (0. ....)	4358	3347	5650	6153	7121
$\hat\beta_4$ (0. ....)	8386	3108	0269	2692	0001
$\hat\beta_5$ (0. ....)	0547	2279	2920	4695	4344
p-value H_0: $\mu = \beta$ (0. ....)	3793	3350	1782	2216	1670
$\overline{\hat v} = 0.$	0994	0896	0770	0623	0449
$\overline{\hat c} = 0.$	0495	0414	0324	0236	0145
number of convergent runnings	200	131	70	19	33
number of formations of BJ-loops	0	69	130	181	167
average iteration number until convergence	3.7	8.1	11.8	22.6	48.7
average length of BJ-loops	-	2.0	2.1	2.5	4.1
computation time in minutes	6	17	23	40	140

Figures 1 - 5: $N = 200$ *groups of related elementary units of* $K_n \equiv 3$ *parallel processes each, data generation and estimation by equicorrelation structure,* $\sigma_\alpha^2 = \sigma_\varepsilon^2 = 0.05 \Rightarrow v = 0.10$, $c = 0.05$, *type II censoring: Standard deviation of the regression estimations (straight lines) and mean of the estimated standard deviations (dashed lines) over* $S = 200$ *simulations vs. censoring rate*

Figure 1: $s(\hat{\beta}_1)$ *(straight line) and* $\overline{\hat{\sigma}(\hat{\beta}_1)}$ *(dashed line) (*β_1*: intercept)*

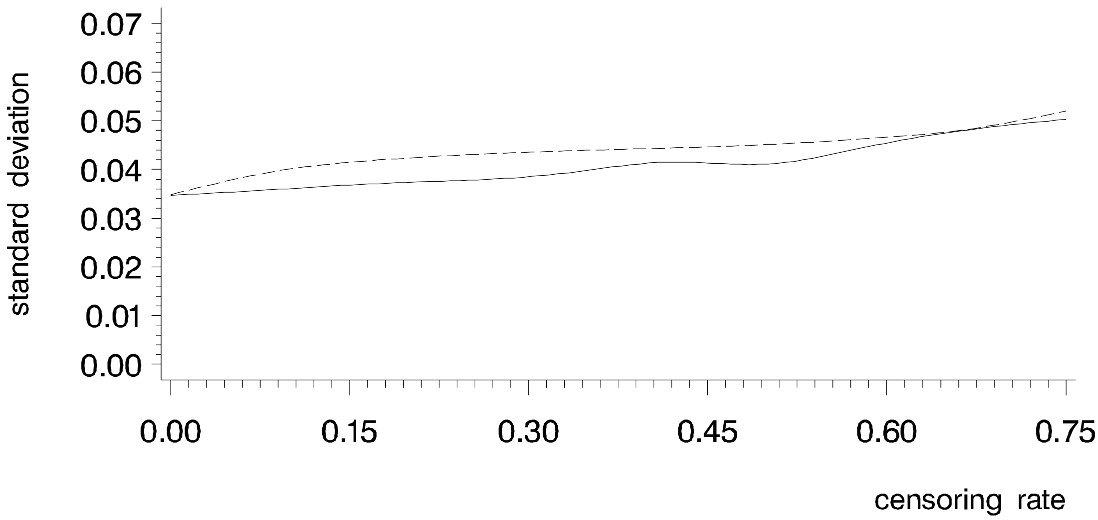


Figure 2: $s(\hat{\beta}_2)$ *(straight line) and* $\overline{\hat{\sigma}(\hat{\beta}_2)}$ *(dashed line)*
(x_2*: constant within block, metric)*

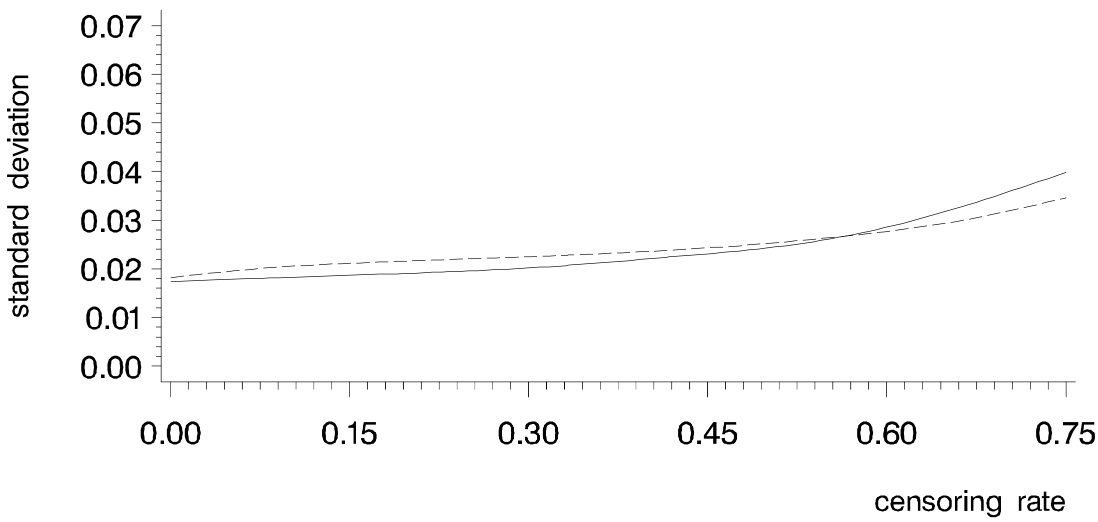


Figure 3: $s(\hat{\beta}_3)$ *(straight line) and* $\overline{\hat{\sigma}(\hat{\beta}_3)}$ *(dashed line)*
(x_3: constant within block, dichotomous)

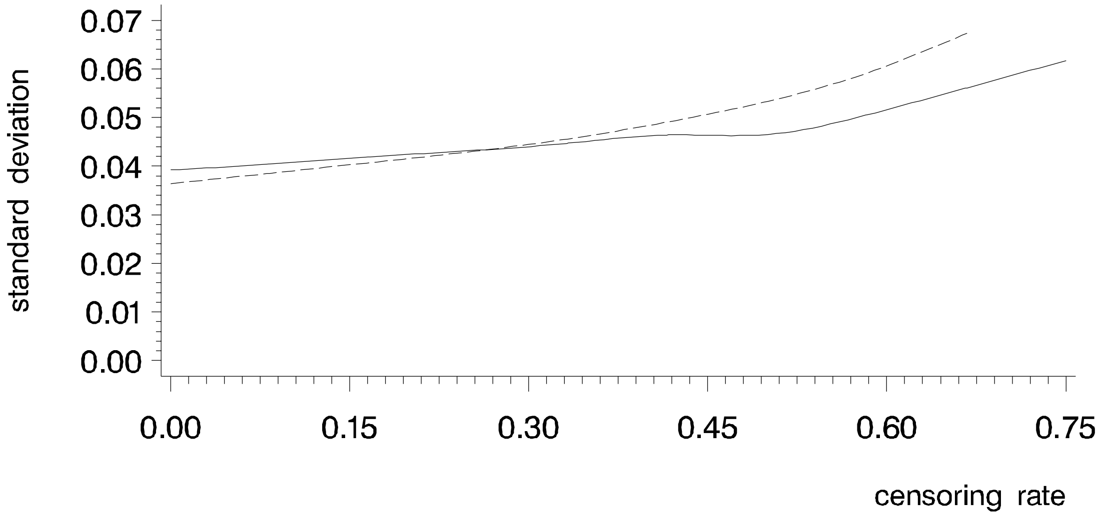


Figure 4: $s(\hat{\beta}_4)$ *(straight line) and* $\overline{\hat{\sigma}(\hat{\beta}_4)}$ *(dashed line)*
(x_4: varying from unit to unit, metric)

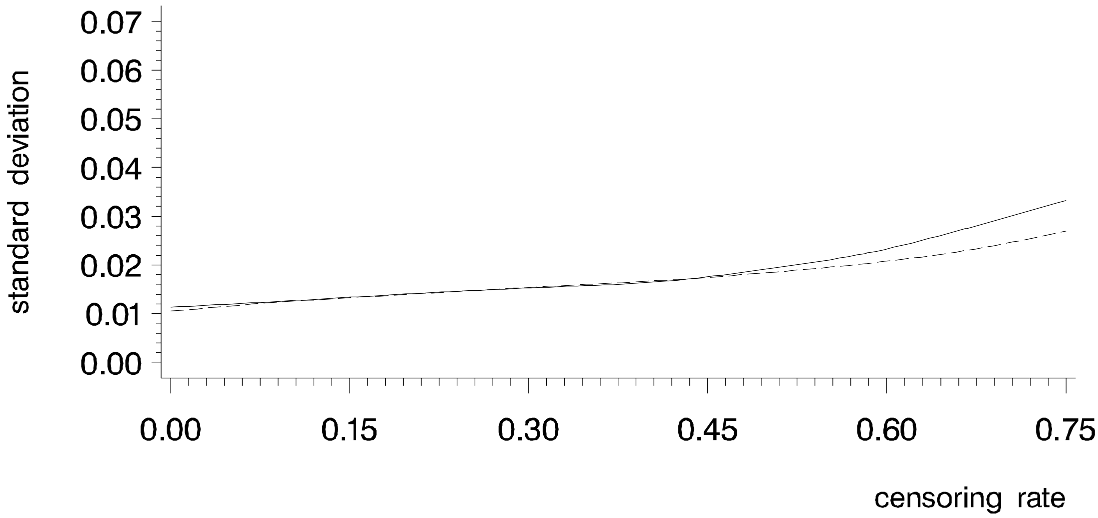
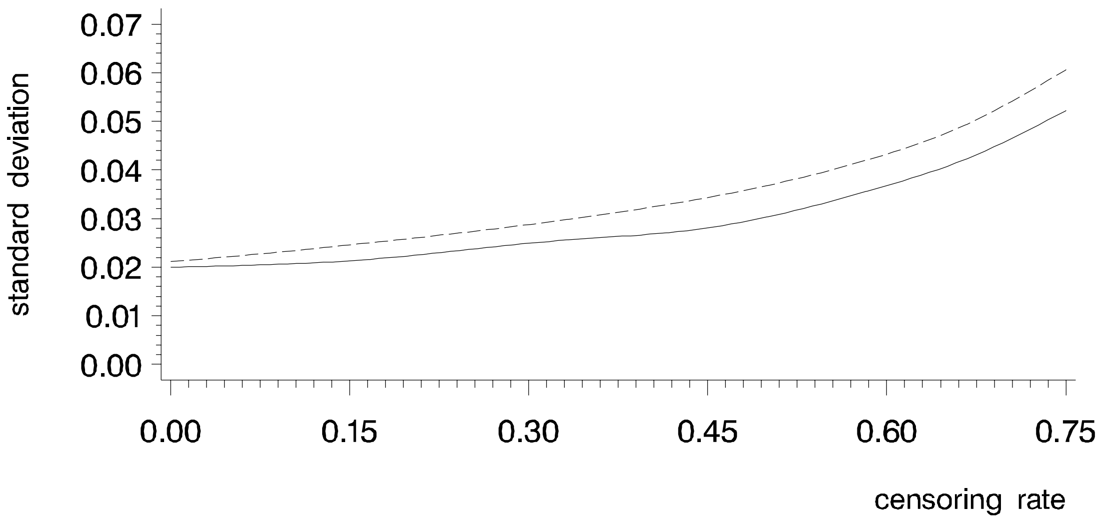


Figure 5: $s(\hat{\beta}_5)$ *(straight line) and* $\overline{\hat{\sigma}(\hat{\beta}_5)}$ *(dashed line)*
(x_5: varying from unit to unit, dichotomous)



the case of an extreme censoring rate). This result was confirmed in all simulations of PPRU as well as in such of SSRE.

Of course, the standard deviations of the estimated parameters and the rmse in their wake increase with higher censoring rates as an effect of less information in the data. Additionally, the differences between the standard deviations and the means of the estimated standard deviations become larger with higher censoring rates and we observe a tendency of over-estimating the variance of the estimators in the case of higher censoring rates whereas the variance seems to be estimated without bias in the absence of censoring. This result is visualized in figures 1 - 5. A starting point for an explanation could be the fact that in reality we misspecify the correlation structure of the y_n^* in the case of censored data as there are different correlations within censored, within uncensored, and between censored and uncensored spells, and the variance of y_{nk}^* is smaller in the censored cases than in the uncensored cases. As a consequence, the moment estimations of v and c decrease with higher censoring rates. In spite of this flaw the results on the whole are quite satisfactory in the case of PPRU.

In table 2 comparable results for the situation of $N = 200$ units with K_n successive spells each are given. Each unit is observed at least for a fixed observation period ($C_n \equiv 16.9$). In the case of SSRE without censoring every unit is observed further on until the momentary spell is completed. In the other case observation is broken off and the last spell of each unit is censored. The number of spells K_n is a random variable but we chose the length of the observation period so that the average number of observations was about 600, the same as in the PPRU case.

In the SSRE case with censoring we recognize a disposition for a moderate bias of the intercept and of the parameters corresponding with spell-varying covariates (β_4 and β_5). This is not the case for parameters corresponding with constant covariates. In spite of that the differences of the values of rmse and the corresponding standard deviations are negligible. These results were confirmed in studies with a higher number of simulations ($S = 500$).

The p-values for the hypothesis of normal distribution (not given in the table) are higher than 0.05 without exception.

We state the same results as in the PPRU case that for censored data the standard deviations of the estimated parameters are higher, the differences to the means of the estimated standard deviations are larger and there is a tendency to over-estimate these standard deviations.

The third group of simulations (table 3) shows the behaviour of the estimator in the SSRE case with various sample sizes. Of course, with increasing sample size the standard deviations of the parameters decrease. In the sequence, the bias of the intercept and of the parameters corresponding with spell-varying covariates becomes more obvious. On the other hand we state quite good properties in the estimation of parameters corresponding with constant covariates and in the case of a small sample size of $N = 50$.

We get similar results when we examine the behaviour of the estimator under various values of σ_α^2 relative to σ_ε^2 and thus of the correlation between y_{nk} and y_{nl}. At fixed $\sigma_\varepsilon^2 = 0.05$ we varied σ_α^2 from 0.01 to 0.25 and got correlations of 1/6 and 5/6 respectively (table 4). In the case of high correlations there is an evident bias of the parameters corresponding with spell-varying covariates. For constant covariates the properties remain good also in the extreme case.

Table 2: $N = 200$ *units with successive spells, separated by recurrent events, data generation and estimation by equicorrelation structure,* $\sigma_\alpha^2 = \sigma_\varepsilon^2 = 0.05 \Rightarrow v = 0.10$, $c = 0.05$, *left column: no censoring, each unit is observed until the last spell (at time* $C_n \equiv 16.9$*) is completed, right column: type I censoring after observation period* $C_n \equiv 16.9$*: Mean, RMSE and standard deviation of the regression estimations, mean of the estimated standard deviations, p-values and convergence statistics over* $S = 200$ *simulations*

censoring	no	yes
$\overline{\hat\beta_1} = 0.\ldots.$	5008	4948
$\overline{\hat\beta_2} = 0.\ldots.$	4995	5005
$\overline{\hat\beta_3} = 0.\ldots.$	4995	5001
$\overline{\hat\beta_4} = 0.\ldots.$	5013	5027
$\overline{\hat\beta_5} = 0.\ldots.$	5001	5013
$RMSE(\hat\beta_1) = 0.\ldots.$	0299	0361
$RMSE(\hat\beta_2) = 0.\ldots.$	0179	0209
$RMSE(\hat\beta_3) = 0.\ldots.$	0361	0420
$RMSE(\hat\beta_4) = 0.\ldots.$	0111	0148
$RMSE(\hat\beta_5) = 0.\ldots.$	0208	0276
$s(\hat\beta_1) = 0.\ldots.$	0299	0358
$s(\hat\beta_2) = 0.\ldots.$	0179	0209
$s(\hat\beta_3) = 0.\ldots.$	0361	0420
$s(\hat\beta_4) = 0.\ldots.$	0111	0146
$s(\hat\beta_5) = 0.\ldots.$	0208	0276
$\overline{\hat\sigma(\hat\beta_1)} = 0.\ldots.$	0349	0460
$\overline{\hat\sigma(\hat\beta_2)} = 0.\ldots.$	0192	0274
$\overline{\hat\sigma(\hat\beta_3)} = 0.\ldots.$	0377	0505
$\overline{\hat\sigma(\hat\beta_4)} = 0.\ldots.$	0105	0157
$\overline{\hat\sigma(\hat\beta_5)} = 0.\ldots.$	0210	0296
p-value H_0: $\mu = \beta$ $(0.\ldots.)$	5281	1093
p-values H_0:		
$\mu_1 = \beta_1$ $(0.\ldots.)$	7167	0426
$\mu_2 = \beta_2$ $(0.\ldots.)$	7065	7262
$\mu_3 = \beta_3$ $(0.\ldots.)$	8490	9849
$\mu_4 = \beta_4$ $(0.\ldots.)$	1032	0083
$\mu_5 = \beta_5$ $(0.\ldots.)$	9619	5188
$\overline{\hat v} = 0.\ldots.$	1007	0752
$\overline{\hat c} = 0.\ldots.$	0547	0367
$\overline{\sum_{n=1}^N K_n}$ (observations)	599.2	599.2
average censoring rate	0	0.334
number of convergent runnings	200	96
number of formations of BJ-loops	0	104
average iteration number until convergence	5.8	9.9
average length of BJ-loops	-	2.2
computation time in minutes	14	27

Table 3: *N units with successive spells, separated by recurrent events, data generation and estimation by equicorrelation structure, $\sigma_\alpha^2 = \sigma_\varepsilon^2 = 0.05 \Rightarrow v = 0.10$, $c = 0.05$, type I censoring after observation period $C_n \equiv 16.9$: Mean, RMSE and standard deviation of the regression estimations, mean of the estimated standard deviations, p-values and convergence statistics over $S = 200$ simulations*

N	50	200	500	1000	2000
$\overline{\hat{\beta}_1} = 0.\ ....$	4812	4948	4961	4955	4951
$\overline{\hat{\beta}_2} = 0.\ ....$	5010	5005	4990	5006	5001
$\overline{\hat{\beta}_3} = 0.\ ....$	5016	5001	4997	5003	5001
$\overline{\hat{\beta}_4} = 0.\ ....$	5037	5027	5016	5019	5020
$\overline{\hat{\beta}_5} = 0.\ ....$	5096	5013	4997	5022	5018
$RMSE(\hat{\beta}_1) = 0.\ ....$	0810	0361	0266	0174	0133
$RMSE(\hat{\beta}_2) = 0.\ ....$	0441	0209	0137	0091	0069
$RMSE(\hat{\beta}_3) = 0.\ ....$	0828	0420	0275	0188	0128
$RMSE(\hat{\beta}_4) = 0.\ ....$	0316	0148	0098	0065	0051
$RMSE(\hat{\beta}_5) = 0.\ ....$	0595	0276	0157	0118	0081
$s(\hat{\beta}_1) = 0.\ ....$	0788	0358	0264	0168	0124
$s(\hat{\beta}_2) = 0.\ ....$	0441	0209	0136	0091	0069
$s(\hat{\beta}_3) = 0.\ ....$	0828	0420	0275	0188	0128
$s(\hat{\beta}_4) = 0.\ ....$	0314	0146	0097	0062	0047
$s(\hat{\beta}_5) = 0.\ ....$	0587	0276	0157	0116	0079
$\overline{\hat{\sigma}(\hat{\beta}_1)} = 0.\ ....$	0941	0460	0292	0205	0146
$\overline{\hat{\sigma}(\hat{\beta}_2)} = 0.\ ....$	0461	0274	0170	0122	0086
$\overline{\hat{\sigma}(\hat{\beta}_3)} = 0.\ ....$	1043	0505	0320	0227	0160
$\overline{\hat{\sigma}(\hat{\beta}_4)} = 0.\ ....$	0305	0157	0099	0070	0050
$\overline{\hat{\sigma}(\hat{\beta}_5)} = 0.\ ....$	0565	0296	0186	0132	0093
p-value H_0: $\mu = \beta \quad (0.\ ....)$	0030	1093	0006	0000	0000
p-values H_0:					
$\mu_1 = \beta_1 \quad (0.\ ....)$	0009	0426	0368	0002	0000
$\mu_2 = \beta_2 \quad (0.\ ....)$	7430	7262	2784	3393	8856
$\mu_3 = \beta_3 \quad (0.\ ....)$	7783	9849	8626	8072	9045
$\mu_4 = \beta_4 \quad (0.\ ....)$	0937	0083	0173	0000	0000
$\mu_5 = \beta_5 \quad (0.\ ....)$	0220	5188	7949	0089	0016
$\overline{\hat{v}} = 0.\ ....$	0706	0752	0751	0750	0750
$\overline{\hat{c}} = 0.\ ....$	0287	0367	0369	0367	0371
$\overline{\sum_{n=1}^{N} K_n}$(observations)	150.4	599.2	1502.2	2995.4	5992.4
average censoring rate	0.335	0.334	0.333	0.334	0.334
number of convergent runnings	78	96	89	99	97
number of formations of BJ-loops	122	104	111	101	103
average iteration number until convergence	9.4	9.9	10.1	10.6	11.1
average length of BJ-loops	2.3	2.2	2.0	2.0	2.0
computation time in minutes	7	27	79	181	948

Table 4: $N = 200$ *units with successive spells, separated by recurrent events, data generation and estimation by equicorrelation structure,* $\sigma_\varepsilon^2 = 0.05$*, type I censoring after observation period* $C_n \equiv 16.9$*: Mean, RMSE and standard deviation of the regression estimations, mean of the estimated standard deviations, p-values and convergence statistics over* $S = 200$ *simulations*

σ_α^2	0.01	0.05	0.25
$\overline{\hat\beta_1} = 0.\ ....$	4987	4948	4945
$\overline{\hat\beta_2} = 0.\ ....$	5007	5005	4961
$\overline{\hat\beta_3} = 0.\ ....$	4970	5001	5004
$\overline{\hat\beta_4} = 0.\ ....$	5004	5027	5089
$\overline{\hat\beta_5} = 0.\ ....$	5000	5013	5092
$RMSE(\hat\beta_1) = 0.\ ....$	0277	0361	0694
$RMSE(\hat\beta_2) = 0.\ ....$	0152	0209	0426
$RMSE(\hat\beta_3) = 0.\ ....$	0303	0420	0820
$RMSE(\hat\beta_4) = 0.\ ....$	0122	0148	0197
$RMSE(\hat\beta_5) = 0.\ ....$	0252	0276	0334
$s(\hat\beta_1) = 0.\ ....$	0277	0358	0692
$s(\hat\beta_2) = 0.\ ....$	0152	0209	0425
$s(\hat\beta_3) = 0.\ ....$	0302	0420	0820
$s(\hat\beta_4) = 0.\ ....$	0122	0146	0176
$s(\hat\beta_5) = 0.\ ....$	0252	0276	0321
$\overline{\hat\sigma(\hat\beta_1)} = 0.\ ....$	0288	0460	0986
$\overline{\hat\sigma(\hat\beta_2)} = 0.\ ....$	0159	0274	0630
$\overline{\hat\sigma(\hat\beta_3)} = 0.\ ....$	0313	0505	1189
$\overline{\hat\sigma(\hat\beta_4)} = 0.\ ....$	0130	0157	0210
$\overline{\hat\sigma(\hat\beta_5)} = 0.\ ....$	0251	0296	0390
p-value H_0: $\mu = \beta$ $(0.\ ....)$	2362	1093	0000
p-values H_0:			
$\mu_1 = \beta_1$ $(0.\ ....)$	5030	0426	2585
$\mu_2 = \beta_2$ $(0.\ ....)$	5294	7262	1986
$\mu_3 = \beta_3$ $(0.\ ....)$	1559	9849	9452
$\mu_4 = \beta_4$ $(0.\ ....)$	6197	0083	0000
$\mu_5 = \beta_5$ $(0.\ ....)$	9836	5188	0001
$\overline{\hat v} = 0.\ ....$	0434	0752	2532
$\overline{\hat c} = 0.\ ....$	0059	0367	2688
$\overline{\sum_{n=1}^N K_n}$(observations)	592.7	599.2	649.4
average censoring rate	0.338	0.334	0.309
number of convergent runnings	100	96	35
number of formations of BJ-loops	100	104	165
average iteration number until convergence	8.8	9.9	14.8
average length of BJ-loops	2.1	2.2	3.0
computation time in minutes	27	27	77

The choice of the working correlation structure

There is remaining one open question: When we analyze an empirical data set we usually do not know if actually there is any correlation within the blocks and if there is, which correlation assumption comes nearest to the real one. By simulation studies we can assess the consequences of misspecifying the correlation structure. As an example, in table 5 we give the simulation results of the SSRE model with $N = 200$ units which was already estimated in tables 2, 3 and 4, but now in comparison to the estimation using the independence assumption.

We learn that this kind of misspecification leads to a bias of a relative high extent for nearly all parameters and to higher standard deviations of the estimations in all cases. Another group of simulations (not documented here) showed that if there is really no correlation in the data, the estimations of the regression parameters and their standard deviations differ only marginally if we specify different working correlation matrices. So it is no mistake to use the `equ` option if we are not sure.

The decision is not so easy if the real correlation structure is a kind of autoregressive process or a mixture of heterogeneity and autoregressive process. But simulations (not documented here) let us suppose that it is the worse case to misspecify an equicorrelation structure as pure AR(1) process than vice versa. So the recommendation for the analysis of empirical data sets is to believe the "`equ`" estimator most.

Summary

With the developed GEE/BJ estimator we have a tool for estimating the regression parameters of constant and spell-varying covariates in an Accelerated Failure Time Model with unobserved heterogeneity when we are not sure about the distributions of the heterogeneity and of the error term and when we are not quite sure about the correlation structure.

The estimator works very well in the case of parallel processes of related elementary units. The simulation studies do not speak against the hypothesis that the estimator is unbiased also in extreme circumstances and for small sample sizes.

In the case of successive spells censored by a total observation period there are some problems in the combination of spell-varying covariates and larger sample sizes or higher correlation between the failure times of one unit.

In all cases with censoring we have to consider a tendency to an over-estimation of the variance of the regression estimators. In the usual t-tests on the significance of the effect of a covariate this over-estimation leads to p-values which are too large. So it can happen that an effect which is present in reality is not recognized as significant by the test.

Nevertheless, in comparison with a maximum likelihood method for estimating the considered model the GEE/BJ method is robust, needs much less computation time and has no numerical problems. A comparison of the properties of both estimation methods with regard to bias and efficiency will be carried out by further simulation studies (Hornsteiner and Hamerle, in preparation).

Table 5: $N = 200$ *units with successive spells, separated by recurrent events, data generation by equicorrelation structure,* $\sigma_\alpha^2 = \sigma_\varepsilon^2 = 0.05 \Rightarrow v = 0.10$, $c = 0.05$, *type I censoring after observation period* $C_n \equiv 16.9$, *left column: estimation by (incorrect) independence assumption, right column: estimation by equicorrelation assumption: Mean, RMSE and standard deviation of the regression estimations, mean of the estimated standard deviations, p-values and convergence statistics over* $S = 200$ *simulations*

working correlation matrix	ind	equ
$\overline{\hat\beta_1} = 0.\ldots.$	4568	4948
$\overline{\hat\beta_2} = 0.\ldots.$	5076	5005
$\overline{\hat\beta_3} = 0.\ldots.$	5082	5001
$\overline{\hat\beta_4} = 0.\ldots.$	5029	5027
$\overline{\hat\beta_5} = 0.\ldots.$	5001	5013
$RMSE(\hat\beta_1) = 0.\ldots.$	0598	0361
$RMSE(\hat\beta_2) = 0.\ldots.$	0265	0209
$RMSE(\hat\beta_3) = 0.\ldots.$	0466	0420
$RMSE(\hat\beta_4) = 0.\ldots.$	0162	0148
$RMSE(\hat\beta_5) = 0.\ldots.$	0307	0276
$s(\hat\beta_1) = 0.\ldots.$	0414	0358
$s(\hat\beta_2) = 0.\ldots.$	0253	0209
$s(\hat\beta_3) = 0.\ldots.$	0459	0420
$s(\hat\beta_4) = 0.\ldots.$	0159	0146
$s(\hat\beta_5) = 0.\ldots.$	0307	0276
$\overline{\hat\sigma(\hat\beta_1)} = 0.\ldots.$	0471	0460
$\overline{\hat\sigma(\hat\beta_2)} = 0.\ldots.$	0280	0274
$\overline{\hat\sigma(\hat\beta_3)} = 0.\ldots.$	0516	0505
$\overline{\hat\sigma(\hat\beta_4)} = 0.\ldots.$	0173	0157
$\overline{\hat\sigma(\hat\beta_5)} = 0.\ldots.$	0334	0296
p-value H_0: $\mu = \beta$ (0. ....)	0000	1093
p-values H_0:		
$\mu_1 = \beta_1$ (0. ....)	0000	0426
$\mu_2 = \beta_2$ (0. ....)	0000	7262
$\mu_3 = \beta_3$ (0. ....)	0128	9849
$\mu_4 = \beta_4$ (0. ....)	0103	0083
$\mu_5 = \beta_5$ (0. ....)	9808	5188
$\overline{\hat v} = 0.\ldots.$	0749	0752
$\overline{\hat c} = 0.\ldots.$	-	0367
$\overline{\sum_{n=1}^N K_n}$ (observations)	599.2	599.2
average censoring rate	0.334	0.334
number of convergent runnings	107	96
number of formations of BJ-loops	93	104
average iteration number until convergence	8.8	9.9
average length of BJ-loops	2.1	2.2
computation time in minutes	24	27

6 Application to defibrillator data

The described methods were applied to a clinical study which contains data of $N = 74$ patients suffering from malign ventricular arrhythmias, an irregularity of the heartbeat. In the terms of this paper it is a typical SSRE data set. The persons have got implanted a defibrillator. This appliance is a kind of cardiac pacemaker but takes action only when necessary. In this case a shock is triggered and the date of this shock is recorded. We take the date of the implantation as the beginning of the first spell together with the beginning of the observation period. The observation ends with the previous control examination of the patient when the collected data could be taken. So we have the total observation period C_n as a random censor value and the last spell is typically censored. We assume that C_n is independent from the failure times and the error terms.

The characteristics of the study population are shown in table 6. The mean of the observation periods is 411 days. There are cases in the data set in which the defibrillator had no reason for a shock all the time, that means one long censored spell. The other extreme is a patient with 30 shocks that means 31 spells in the observation period. The average is about four spells per patient that means a censoring rate of about 25%.

The data set further contains ten covariates partly taken from medicinal examinations like a 24-hours-electrocardiogram which in general describe the risk of the patient (see table 7). They are treated as constant over the observation period. Four of them are metric, four others are counting variables, one (MED) is dichotomous and one (EPU) is nominally scaled in five categories (and was transformed in dummy variables). We want to give an answer to the question which of the covariates have an effect on the occurrence of the shocks. To be more concrete, we apply the discussed Accelerated Failure Time Model with unobserved heterogeneity to the data and expect results about the significance of the given covariates in modeling the lengths of the spells between every two shocks.

Table 6: *Characteristics of defibrillator data*

	cases	mean	std dev	min	max	
number of spells K_n	74	3.9	5.0	1	31	
observation period C_n (days)	74	411	308	4	1244	
spell c_{nk} (days)	286	106	181	1	1107	
KHK	68	1.75	1.33	0	3	
EF (%)	67	42.1	18.6	15	84	
VES	74	3267	7954	1	51691	
COUPLET	74	115	407	0	3288	
VTACHY	74	8.49	29.8	0	192	
ASIN	72	0.198	0.135	-0.029	0.714	
AVES	65	2.59	0.88	0.25	4.03	
SDNN	73	118	52.3	29.9	370	
MED		1	0			
	64	37.5%	62.5%			
EPU		NA	VT	VF	SVT	VHF
	63	27.0%	65.1%	9.6%	1.6%	3.2%

Table 7: *Covariates in defibrillator data and p-values of univariate analyses*

covariate	explanation	p-values
EF	left ventricular ejection fraction (metric)	0.267
KHK	coronary heart disease (0/1/2/3)	0.199
VES	number of ventricular premature complexes in 24 hours	0.047
COUPLET	number of couplets in 24 hours	E-6
VTACHY	number of salvos in 24 hours	0.030
ASIN	αSin (metric)	0.832
AVES	αVES (metric)	0.585
SDNN	(metric)	0.874
MED	medication (1: yes/ 0: no)	0.418
EPU	result of electro-physiological examination in five categories:	
EPUNA	dummy for "no arrhythmias"	0.446
EPUVT	dummy for "ventricular tachycardie"	0.890
EPUVF	dummy for "ventricular fibrillation"	0.866
EPUSVT	dummy for "supra-ventricular tachycardie"	E-10
EPUVHF	dummy for "atrial fibrillation"	E-8

There are dispersed missing values in the design matrix so that it is impossible to estimate a model with all the covariates in a complete case analysis. Assuming that the values are missing at random we did a stepwise forward selection and in each step we included as many cases as possible. In table 6 for each covariate the number of patients (cases) is given where it is not missing.

The beginning of the forward selection is the computing of F-to-enter-values for each of the 14 covariates. In the first step we have 14 models of the kind

$$y_{nk} = \ln T_{nk} = \beta_0 + \beta_p x_{nkp} + \sigma_\alpha \alpha_n + \sigma_\varepsilon \varepsilon_{nk},$$

$n = 1, \ldots, 74$, $k = 1, \ldots, K_n$, T_{nk} the (partly observed) failure times and $p = 1, \ldots, 14$, the covariates of tables 6/7. We apply the GEE/BJ method specifying the working matrix of equicorrelation type. The resulting p-values of the univariate t-tests on the hypothesis that $\beta_p = 0$, $p = 1, \ldots, 14$ correspond to the F-to-enter-values of the first step. They are given in the right column of table 7.

The results show that the covariates EPUVT, SDNN, EPUVF, ASIN, AVES, MED, EF and KHK seem to have no or just little effect on the lengths of the spells whereas EPUSVT, EPUVHF, COUPLET, VTACHY and VES (in this order) are candidates for a model with significant covariates.

Further analyses with various combinations yield that with entering the second covariate the stepwise selection in every case comes to the end. A third covariate is in no case significant. The results showed that the five candidates can be divided into two groups: EPUSVT is significant in every combination with one of the four others, whereas COUPLET, EPUVHF, VTACHY and VES seem to be correlated so that the inclusion of one of them excludes the others.

Finally, the model which is the one with the lowest p-values contains COUPLET and EPUSVT. The estimation results applying the GEE/BJ method with equicorrelation structure are given in the left column of table 8.

Table 8: *Estimation results of defibrillator data: Estimated regression parameters, estimated standard deviations, p-values and moment estimations of the GEE/BJ method with three specifications of the working correlation matrix*

	equ	ind	ar1
$\hat{\boldsymbol{\beta}}$			
CONST	5.23	3.53	3.76
COUPLET	-0.000859	-0.000211	-0.000236
EPUSVT	-2.48	-0.775	-0.992
$\hat{\boldsymbol{\sigma}}(\hat{\boldsymbol{\beta}})$			
CONST	0.258	0.375	0.372
COUPLET	0.000145	0.000263	0.000265
EPUSVT	0.378	0.416	0.429
p-values			
CONST	E-29	E-13	E-14
COUPLET	E-7	0.426	0.377
EPUSVT	E-8	0.067	0.024
$\hat{v}$	6.04	4.84	4.83
$\hat{c}$	3.83	-	-
$\hat{\rho}$	-	-	0.204

Basing on the analyzed dataset it is shown that patients with a high number of couplets in a 24-hours-electrocardiogram and/or supra-ventricular tachycardie in the electro-physiological examination have a definitely higher risk of short spells between the shocks than patients with a low number of couplets and/or other results in EPU (with the exception of atrial fibrillation). The estimated variance and covariance of the spells of one patient give a correlation of about 0.6 that means the assumption of the equicorrelation matrix seems plausible in comparison to the independence assumption. The correctness of the results is based on the simulation studies in the case of a low sample size, a medium correlation and especially time-constant covariates.

The results should be interpreted with some caution. We have to consider that the standard deviations of the regression parameters are tendencially over-estimated. So it is possible that the effects are a bit higher than we recognize by looking just at the p-values. Beyond that, the relative small sample size may be responsible if we do not detect effects which are present in reality. On the other hand the small sample size is the reason that some outliers in the data influence the observed significances. Additionally, significance disappears or becomes weaker when we use the independence or the AR(1) working correlation matrix as we have higher estimated standard deviations in these cases. But this fact could also be interpreted as a sign that the equicorrelation assumption is more plausible.

Further studies will be carried out with a more detailed dataset containing demographic covariates and more precise information about medication. We also plan the inclusion of time-dependent covariates so that the workday or seasonal influence on ventricular arrhythmias (see e.g. Peters et al., 1996) can be investigated in the context of the described model.

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