An overview of methods for interval-censored data with an emphasis on applications in dentistry

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An overview of methods for interval-censored data with an emphasis on applications in dentistry

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Interval-censored time-to-event data occur in many medical areas, with dentistry or AIDS research being typical representatives. This article reviews methods for the analysis of such data, with an emphasis on the use of the accelerated failure time (AFT) model. A flexible AFT model (avoiding parametric assumptions on the distribution of the error term) is described in greater detail and is used to solve a typical dental question in a longitudinal oral health study.

1 Introduction

Standard survival methods assume that individuals are followed over time for the occurrence of a specific event. The time to the event is referred to as duration time. If at the end of the observation period the event has not been observed, the time to the event is called 'right censored'. However, in dentistry (and other areas of medical research), the occurrence of the event of interest can often be recorded only at planned (or unplanned) visits, which gives rise to 'interval-censored data'. A typical example is the time to caries or to emergence of a tooth. Indeed, in case of a cavity or of emergence, the event is often observed after some delay, say at planned (or even unplanned) visits.

For right-censored data, a battery of statistical tests and techniques is available to tackle most research questions under a variety of statistical assumptions. Also, commercial software is available for many procedures. For interval-censored data, statistical techniques are less well developed and their statistical properties are much more complex. But above all, almost no (commercial) software is available.

In this article, first the current statistical methods on interval-censored data are reviewed. Then, a recently developed survival method is described, which is useful for interval-censored data and operates under mild statistical assumptions.

To proceed, some notation is needed. Let T_i $(i = 1, \ldots, n)$ be the random variable recording the duration time of the ith individual in the sample. With interval-censored data, instead of T_i, only the intervals $[L_i, R_i]$ are observed, where $L_i \leq T_i \leq R_i$. This does not rule out exactly observed, right-censored and left-censored data for which $L_i = R_i = T_i$, $R_i = \infty$ and $L_i = 0$, respectively. Often, additionally, a vector $\boldsymbol{x}_i$ of

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covariates ($i = 1, \ldots, n$) is recorded. A typical question is then whether the distribution of T_i depends on the covariates.

To illustrate the analyses, the Signal Tandmobiel® study is considered. It is a longitudinal dental study performed in Flanders in 1996–2001 involving 4468 schoolchildren (2315 boys and 2153 girls) born in 1989, who were annually examined by one of the 16 dentists. More on the design of the study can be found in Vanobbergen *et al.*[1] In this article, the focus is on the distribution of emergence times of permanent maxillary right premolars (teeth 14 and 15 in European dental notation). Adequate knowledge of timing and patterns of tooth emergence is useful for diagnosis and treatment planning in paediatric dentistry and orthodontics. Obviously, the distribution of emergence times of a particular tooth is different for boys and girls. For that reason, the covariate gender (0 for boys and 1 for girls) is used in our models. Additionally, it was of dental interest to check whether the distribution of the emergence time of a permanent tooth changes when the primary predecessor of the permanent tooth was caried. For this, a binarized dmf score pertaining to the predecessor as a covariate is included, dmf = 1 if the primary predecessor of that permanent tooth was decayed or missing owing to caries or filled and 0 otherwise. Owing to the design of the study (annual planned examinations), the response variable – time to the emergence of a particular tooth – is interval-censored, with intervals of length equal to approximately 1 year.

For each tooth separately, the following typical goals in survival analysis are of interest: 1) Estimate the survival function $S(t|\boldsymbol{x}) = P(T > t|\boldsymbol{x})$ or equivalently the cumulative distribution function (cdf) $F(t|\boldsymbol{x}) = 1 - S(t|\boldsymbol{x})$. In the context of tooth emergence, the cdf is known as the emergence curve. 2) Compare the distributions of emergence time of two populations specified by two different covariate vectors (e.g., compare children with sound and decayed primary teeth or boys and girls). 3) Set up a regression model to describe the distribution of emergence time for populations with different values of covariates.

In Section 2, some methods that address the aforementioned questions in the context of interval censoring are reviewed. In this aspect, the focus is on the accelerated failure time (AFT) model, which is the competitor of the more widely used proportional hazards (PH) model. Section 3 briefly describes the flexible AFT model of Komárek *et al.*,[2] which can be used for the analysis of the interval-censored data without making strong distributional assumptions. In Section 4, the use of this model is illustrated using the Signal Tandmobiel® data. In the final section, future research is indicated.

2 Review of methods for interval-censored data

A variety of methods (non-, semi- and fully parametric) for right-censored data have been developed. Further, commercial software is available to support the techniques. In contrast, for interval-censored data, commercial software seems to be available only for non-parametric estimation of survivor curves and for parametric modelling, besides the user-written programs. Further, until recently, only few methods were available. Therefore, in practice, modelling with interval-censored data is often mimicked by methods developed for right-censored data. For this, the interval needs to be replaced by

an exact time. The most common assumption is that the event occurred at the midpoint of the interval. However, applying methods for right-censored data on this artificial fixed points can lead to biased and misleading results.[3–6] This article overviews appropriate methods to deal with interval-censored data and links them to the corresponding (classical) method for right-censored data.

2.1 Estimation of survival/cdf

The classical non-parametric method is given by Kaplan and Meier.[7] Its interval-censored data counterpart was first proposed by Peto.[8] Turnbull[9] improved the numerical algorithm to estimate the survival function using his so-called iterative self-consistency algorithm, which is, in fact, an EM type[10] of algorithm. Nowadays, it is implemented in the S-PLUS function `kaplanMeier`.

A valuable alternative to non-parametric procedures is obtained by smoothing the survival or equivalently the density function or the hazard function. In situations where it can be assumed that the event times are continuously distributed, more realistic, not stepwise, estimates are also obtained. One such method, directly applicable to both right- and interval-censored data is given by Kooperberg and Stone,[11] who smooth the density using splines and also provide software S-PLUS library `splinelib` downloadable from *StatLib*. Use of splines in the smoothing of the hazard function is then used by the approach of Rosenberg.[12]

2.2 Comparison of two survival distributions

For right-censored data, many non-parametric tests for comparing two survival curves are available, for example, the log-rank test,[13] the Gehan generalization of the Wilcoxon test,[14] the Peto–Prentice generalization of the Wilcoxon test[15,16] and the weighted Kaplan–Meier statistic.[17]

The Gehan–Wilcoxon test has been adopted to interval-censored data by Mantel,[18] whereas the interval-censored version of the Peto–Prentice–Wilcoxon test is presented by Self and Grossmann.[19] The log-rank test for interval-censored data is given by Finkelstein.[20] Further, Petroni and Wolfe (1994)[21] discuss the weighted Kaplan–Meier statistic in the context of interval censoring. Finally, Fay[22] derives a general class of linear-rank tests for interval-censored data, which covers, as special cases, the Wilcoxon-based tests.

Regrettably, the asymptotic properties of the aforementioned methods assume the grouped continuous model, which implies that the status of each subject is checked at the same timepoints (in the study time scale) whose number is fixed or that observed intervals are grouped in such a way. For our dental application, it would mean that the emergence status of the teeth was checked at prespecified ages, the same for all children. Obviously, such setting is very restrictive in many practical situations. For example, a particular child was checked by a dentist on a prespecified day of the year, irrespective of the child's age.

The grouped continuous model assumption is necessary to be able to apply standard maximum likelihood theory to interval-censored data measured on a continuous scale without making any parametric assumptions. Only recently, Fang *et al.*[23] developed

a test statistic on the basis of the weighted Kaplan–Meier statistic of Pepe and Fleming,[17] which does not require the grouped continuous model assumption. Finally, Pan[24] offers two-sample test procedures obtained by combining standard right-censored tests and multiple imputation that allows, in contrast to single (e.g., midpoint) imputation mentioned at the beginning of this section, to draw appropriately the statistical inference.

Unfortunately, none of the approaches described here is available in any commercial statistical package.

2.3 PH regression model

The PH model[25] is the most popular regression model for right-censored data. For a given covariate vector $\boldsymbol{x}$, the hazard function $h(t|\boldsymbol{x}) = \lim_{\mathrm{d}t \to 0_+} P(t \leq T < t + \mathrm{d}t | T \geq t, \boldsymbol{x})/\mathrm{d}t$ is expressed as the product of an unspecified baseline hazard function $h_0(t)$ and the exponential of a linear function of the covariates, that is,

$$h(t|\boldsymbol{x}) = h_0(t) \exp(\boldsymbol{\beta}'\boldsymbol{x}) \tag{1}$$

The regression parameter vector $\boldsymbol{\beta}$ is estimated by maximizing a partial likelihood[26] which treats h_0 as nuisance and does not estimate it. However, when the baseline hazard h_0 is of interest as well, for example, for prediction purposes, its non-parametric estimate can be obtained using the method of Breslow.[27]

To extend the PH model to interval-censored data, basically four types of approaches can be found in the literature. First, the baseline hazard h_0 can be parametrically specified and standard maximum likelihood theory applied to estimate the regression parameters. However, the parametric assumptions can cause bias in inference if incorrectly specified.

A second class of methods makes use of a combination of multiple imputation and methods for right-censored data.[28–31] However, a disadvantage of these methods is that they are highly computationally demanding and the fact that the procedures they use to impute missing data have a relatively ad hoc nature.

A third approach suggested by Finkelstein[20] and Goetghebeur and Ryan[32] resembles most the method of Cox[25] combined with that of Breslow.[26] Indeed, in both papers, the baseline hazard h_0 is estimated non-parametrically on top of estimating the regression coefficients. Although the method of Finkelstein relies on the grouped data assumption, Goetghebeur and Ryan developed an EM-type procedure that relaxes that assumption. Moreover, the second approach seems to be the only one that reduces to a standard Cox model when interval censoring reduces to right censoring ($R_i = \infty$).

Finally, methods that smoothly estimate h_0 are a trade-off between parametric modelling that allows for a straightforward maximum likelihood estimation of the parameters and semi-parametric models with a completely unspecified baseline hazard h_0. Kooperberg and Clarkson[33] suggest regression splines, whereas Betensky *et al*.[34] use local likelihood smoothing to model the baseline hazard. An advantage of these methods is that predictive survival and hazard curves are directly available, and, moreover, they are smooth rather than stepwise as in the case of semi-parametric estimation. The software for the approach of Kooperberg and Clarkson is included in the previously mentioned S-PLUS library `splinelib`.

2.4 AFT model

A useful, but less frequently used alternative to the PH model is the AFT model. In this case, the effect of a covariate is an acceleration or deceleration of the event time. For a vector of covariates $\boldsymbol{x}$, the effect is expressed by the parameter vector $\boldsymbol{\beta}$ in the following way:

$$T = \exp(\boldsymbol{\beta}'\boldsymbol{x})\tau \tag{2}$$

where τ is a baseline survival time. On the logarithmic scale, this model becomes a simple linear regression model

$$\log(T) = \boldsymbol{\beta}'\boldsymbol{x} + \varepsilon \tag{3}$$

with $\varepsilon = \log(\tau)$. Usually one assumes that the random variable ε has a density $f^*(e)$ from the location-scale family, that is, $f^*(e) = \sigma^{-1} f\{\sigma^{-1}(e - \alpha)\}$, where $f(\cdot)$ has location parameter 0 and scale parameter 1; α is a location parameter and σ a scale parameter.

A parametric AFT model assumes that $f(e)$ is a density of a specific type (e.g., normal, logistic or Gumbel). In that case, the parameters α, σ and $\boldsymbol{\beta}$ can be estimated easily using maximum likelihood techniques even with interval-censored data, for example, `survreg` in R, `SurvReg` in S-PLUS or `lifereg` in SAS. Evidently, the parametric assumptions affect the shape and character of the resultant survival or hazard curves, which, in the case of an incorrect specification, is undesirable, especially when prediction is of interest.

In contrast, semi-parametric procedures for the AFT model leave the density $f^*(e)$ unspecified and provide only the estimate of the regression parameter vector $\boldsymbol{\beta}$. The whole class of these methods for right-censored data based on linear-rank tests is described comprehensively by Kalbfleisch and Prentice.[35] Their extension to interval censoring was studied by Rabinowitz *et al*.[36] and Betensky *et al*.[37] Though, both approaches are practically applicable only with low-dimensional covariate vectors $\boldsymbol{x}$. Furthermore, in contrast to the PH model where for right-censored data the baseline hazard can be estimated non-parametrically,[27] no similar approach is available for the AFT model, which implies that semi-parametric procedures cannot be used when prediction is of interest.

Approaches based either on multiple imputation[38,39] or on its combination with smoothing[40] constitute more promising alternatives. The methods of the mentioned papers are applied in the context of multivariate survival data; however, their application to the univariate data is straightforward.

Recently, Komárek *et al*.[2] suggested and implemented a maximum likelihood-based approach for the AFT model that exploits penalized smoothing of the baseline density $f^*(e)$. As such, the method offers both estimates of regression parameters and the baseline density without making any strong parametric assumptions. As a consequence, realistic estimates of survival or hazard curves can be easily obtained. In Section 3, this method is described briefly and in Section 4, the method is applied to the Signal Tandmobiel® data.

2.5 AFT model versus PH model

Both the PH and the AFT models make an explicit assumption about the effect of covariates on the hazard function. The effect of covariates on the hazard function in the PH model is given in Equation (1). For the AFT model, the hazard function of the random variable $T = \exp(\boldsymbol{\beta}'\boldsymbol{x})\tau$ is

$$h(t|\boldsymbol{x}) = \exp(-\boldsymbol{\beta}'\boldsymbol{x}) h_0 \left\{\exp(-\boldsymbol{\beta}'\boldsymbol{x})\ t\right\} \tag{4}$$

The assumed different effect of a covariate on the baseline hazard for the PH and AFT models is exemplified in Figure 1. It is seen that in the AFT model, the effect of covariates on the baseline hazard function is multiplicative, as in the PH model, and on top of that, the effect of covariates is acceleration or deceleration of the time scale. Second in the AFT model, the hazard is increased for $\boldsymbol{\beta} < 0$, whereas in the PH model the hazard increases with $\boldsymbol{\beta} > 0$.

Further, it is generally true that it is not always possible (e.g., due to lack of knowledge) to include all relevant covariates in the model. One of the advantages of the AFT model is that the regression parameters of the included covariates do not change when other, important, covariates are omitted. Of course, the neglected covariates have an impact on the distribution of the error term ε, which is typically changed into one with larger variability. Such change, however, is of no importance (except that it influences the precision with which the regression parameters of the included covariates are estimated) when semi-parametric or smoothing methods are used. Unfortunately, a similar property does not hold for the PH model.[41]

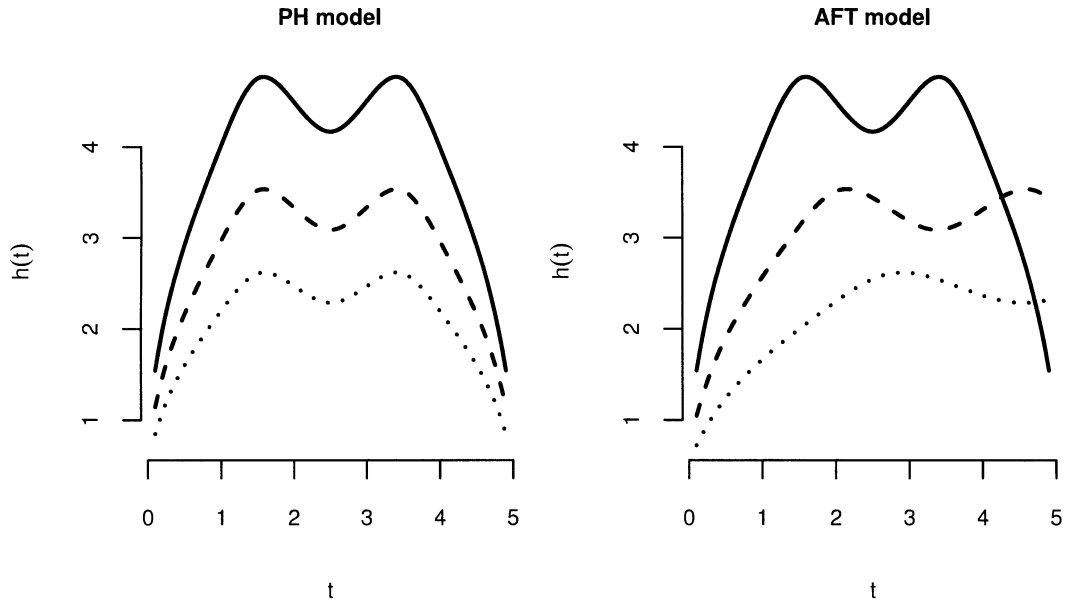

Figure 1 Effect of PH and AFT assumption on a hypothetical baseline hazard function (solid line) for a univariate covariate x taking a value of 0.6 (dashed line) and 1.2 (dotted line), with regression parameter $\beta = -0.5$ for the PH model and $\beta = 0.5$ for the AFT model.

3 Penalized AFT model

It seems that, in contrast to the PH model, it is much more difficult to develop methods for the AFT model with censored data which leave the baseline distribution completely unspecified and at the same time allow for inclusion of a high number of covariates and offer tools to compute predictive survival or hazard curves. In contrast, it is obvious that parametric methods do not offer enough flexibility to correctly model survival data. Penalized smoothing forms a trade-off between the aforementioned two approaches. Indeed, a density or hazard of the baseline distribution using a large basis of parametric functions profits from the advantages of parametric methods while leaving the baseline distribution in practice largely unspecified. Among other things, this implies that prediction is easily accomplished.

The penalized AFT model of Komárek *et al.*[2] was motivated by the P-spline smoothing approach of Eilers and Marx[42] applied to the error density $f(e)$ in model (3). However, for reasons given in Komárek *et al.*,[2] it was decided to replace P-splines by normal densities which result in model (3) with

$$f(e) = \sum_{j=1}^{k} c_j \, \varphi_{\mu_j, \sigma_0^2}(e) \tag{5}$$

where $\varphi_{\mu_j,\sigma_0^2}(\cdot)$ is the normal density with mean μ_j and variance σ_0^2. The number of components k in expression (5) is fixed, but high (say around 30) to offer enough flexibility in the resulting density $f(e)$. The means $\mu_1, \ldots, \mu_k$ are fixed and play the role of knots in P-spline smoothing. These knots are assumed equidistant and to constitute a fine grid. The last fixed parameter of the model is the so-called basis standard deviation, σ_0. Further technical details can be found in Komárek *et al.*[2]. The model (3) with expression (5) will be called the mean penalized AFT model.

The regression parameters $\boldsymbol{\beta}$, the intercept α, the scale σ and the weights c_j, $j = 1, \ldots, k$ are estimated by maximizing the penalized log-likelihood equal to the log-likelihood plus a penalty term to control the smoothness of the estimate of the error density $f(e)$. Asymptotic properties of the resulting estimates that serve as a basis for the inference are given in Komárek *et al.*[2] Finally, different models can be compared by Akaike's information criterion (AIC)[43] with higher values indicating a better fitted model.

In most regression models, it is conventionally assumed that the covariates influence the mean, but it is presumed that it will not influence the scale parameter. With hindsight, this is simply a model choice and in many cases it may be untenable. Recently, there is an interest in joint mean-covariance models in the context of longitudinal studies.[44,45] The original penalized AFT model of Komárek *et al.*[2] can be generalized in the same direction, yielding the mean-scale penalized AFT model. With this generalization, the scale parameter σ is allowed to depend on a vector of covariates, say $\boldsymbol{z}$, as

$$\sigma \equiv \sigma(\boldsymbol{z}) = \exp(\gamma_0 + \boldsymbol{\gamma}'\boldsymbol{z}) \tag{6}$$

For estimation of parameters γ_0 and $\boldsymbol{\gamma}$, the method of penalized maximum likelihood used for the original mean penalized AFT model had to be adjusted only slightly.

Finally, it is pointed out that the software to fit both mean and mean-scale penalized AFT models is available as a contributed package `smoothSurv` of the statistical package R (free clone of S-PLUS) and is downloadable from its web page `http://www.R-project.org`.[46]

4 Analysis of the Signal Tandmobiel® data

The penalized AFT models can be used to tackle the questions posed in Section 1 for the Signal Tandmobiel® data. For the sake of illustration, only teeth 14 and 15 will be considered. Further, the question for these teeth is tackled separately, that is, ignoring their correlation.

As a response, for a particular child, the age of the emergence of a particular permanent tooth (14 or 15), recorded in years, is considered. For a better fit, the time origin of the AFT model is shifted to 5 years of age, that is, by replacing T by $T - 5$ in the AFT model specification (3). Four mean penalized AFT models and two mean-scale penalized AFT models described in Table 1 were fitted. AIC for these models are given in Table 2.

First, the model with the interaction term gender $*$ dmf seems to fit the data best and the interaction term cannot be omitted. Secondly, the models in which the scale parameter σ depends on covariates give a better fit, but for this, only dmf seems to be necessary. These findings lead us to conclude that the model that describes the data satisfactorily well while being kept as simple as possible is the model gender $*$ dmf/scale(dmf).

Table 1 Description of fitted models

Model	Covariate $\boldsymbol{x}$	Covariate $\boldsymbol{z}$
gender	(gender)	–
dmf	(dmf)	–
gender + dmf	(gender, dmf)′	–
gender $*$ dmf	(gender, dmf, gender $*$ dmf)′	–
gender $*$ dmf/scale(dmf)	(gender, dmf, gender $*$ dmf)′	(dmf)
gender $*$ dmf/scale(gender $*$ dmf)	(gender, dmf, gender $*$ dmf)′	(gender, dmf, gender $*$ dmf)′

Table 2 AIC for different models

Model	Tooth 14	Tooth 15
gender	−5532.59	−4551.57
dmf	−5538.03	−4549.93
gender + dmf	−5494.51	−4526.85
gender $*$ dmf	−5491.47	−4522.76
gender $*$ dmf/scale(dmf)	−5468.61	−4506.66
gender $*$ dmf/scale(gender $*$ dmf)	−5467.67	−4507.59

Table 3 Estimates (standard errors) for the model gender $*$ dmf/scale(dmf)

Parameter	Tooth 14	Tooth 15
α	1.7734 (0.0073)	1.9143 (0.0091)
β(gender)	−0.0931 (0.0099)	−0.0803 (0.0110)
β(dmf)	−0.0990 (0.0116)	−0.0773 (0.0125)
β(gender $*$ dmf)	0.0401 (0.0166)	0.0473 (0.0172)
γ_0	−1.5613 (0.0219)	−1.6121 (0.0351)
γ(dmf)	0.2144 (0.0307)	0.2415 (0.0399)

The estimates for this model are given in Table 3. It is seen that dmf $= 1$ accelerates the emergence for both genders and also increases the variability of the emergence distribution.

4.1 Predictive curves

The penalized AFT model has actually a parametric nature, given the weights $c_1, \ldots, c_k$ in expression (5) are known. This makes it easy to compute predictive emergence curves or predictive hazards or densities for a given combination of covariates, say $\boldsymbol{x}^*$ and $\boldsymbol{z}^*$. For instance, the predictive emergence curve is given by the relationship

$$\hat{F}(t|\boldsymbol{x}^*, \boldsymbol{z}^*) = \sum_{j=1}^{k} \hat{c}_j \Phi_{\mu_j, \sigma_0^2} \left(\frac{\log(t) - \hat{\alpha} - \hat{\boldsymbol{\beta}}' \boldsymbol{x}^*}{\hat{\sigma}(\boldsymbol{z}^*)} \right) \tag{7}$$

where $\Phi_{\mu_j, \sigma_0^2}(\cdot)$ denotes a cdf of $N(\mu_j, \sigma_0^2)$. Predictive hazards or densities can be derived from Equation (7).

For the data of this study, predictive emergence curves based on the model gender $*$ dmf/scale(dmf) are shown in Figure 2 and predictive hazards in Figure 3. Further, Figure 2 also shows the non-parameric estimates of Turnbull[9] computed separately for each combination of covariates. It is seen that model-based emergence curves agree with the non-parametric estimates, indicating the goodness-of-fit of our model. Further, the figures show that the difference between children with dmf $= 0$ and dmf $= 1$ is higher for boys than for girls and that the emergence process for boys is indeed postponed when compared with girls.

Non-decreasing predictive hazard curves reflect the nature of the problem at hand. Indeed, it can be expected that, provided the tooth of a child has not emerged yet, the probability that the tooth will emerge increases with age.

4.2 Comparison of emergence distributions between different groups

Although the model, gender $*$ dmf/scale(dmf) gives a parsimonious description of emergence distributions for different groups of children and serves as a solid basis for prediction as was shown in Section 4.1, it is not suitable to provide simple P-values for a comparison of emergence distributions between, for example, boys and girls. Owing to the fact that an interaction term gender $*$ dmf appeared to be significantly important,

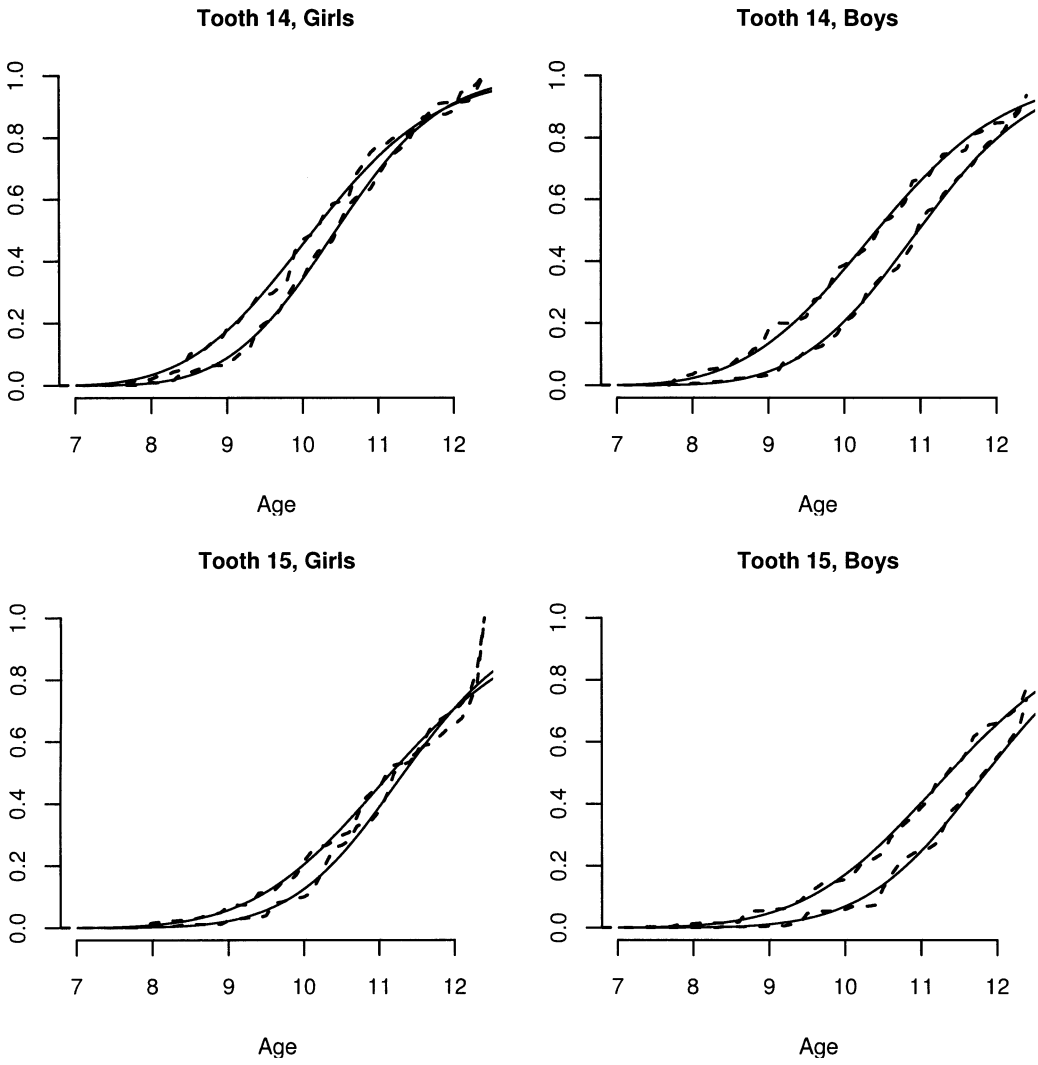

Figure 2 Predictive emergence curves: solid lines for curves based on the model gender $*$ dmf/scale(dmf) (on each plot: left curve for dmf = 1, right curve for dmf = 0) and dashed line for a non-parametric estimate of Turnbull.

only a *P*-value for a multiple comparison of the four groups (girls with dmf = 1 and 0 and boys with dmf = 1 and 0) could be provided.

To simply compare two distributions while averaging the effect of other covariates, the mean AFT model with a univariate covariate x (i.e., either the model gender or the model dmf) can be used together with a significance test for the group parameter. Additionally, it is possible to perform a test that compares two groups while controlling for additional confounding variables (e.g., comparison of boys and girls while controlling for dmf or

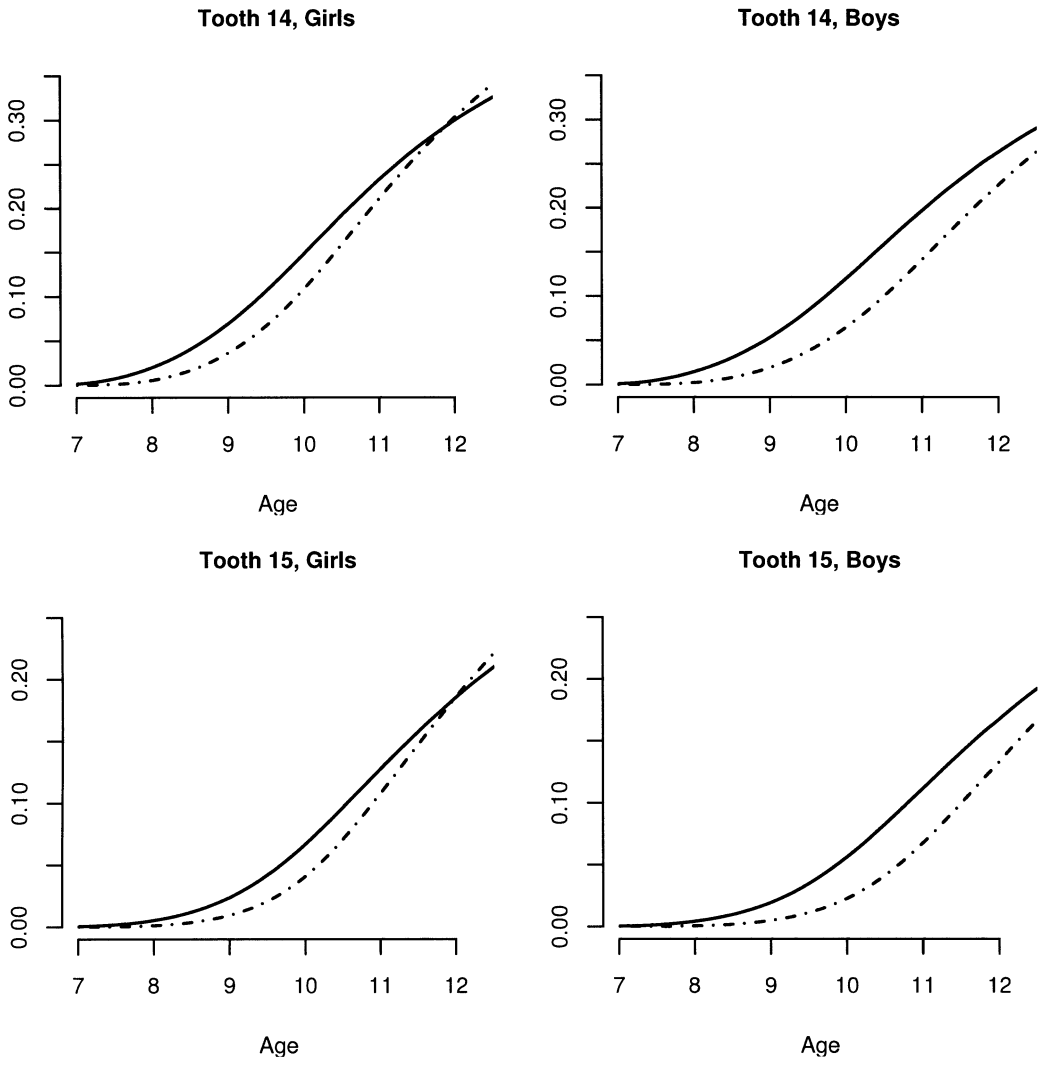

Figure 3 Predictive hazard curves of emergence based on the model gender ∗ dmf/scale(dmf): solid line for dmf = 1 and dotted-dashed line for dmf = 0.

vice versa). To do that, the significance tests of $\boldsymbol{\beta}$ parameters in the model gender + dmf are performed.

The estimates of regression parameters $\boldsymbol{\beta}$ together with their standard errors in mentioned models are given in Table 4. The Wald tests of significance of each β parameter yield all P-values <0.0001, which confirm the findings obtained previously that there is indeed a significance difference in emergence distributions of studied teeth between boys and girls and also between the group of children with dmf = 0 and dmf = 1. The difference remains both marginally and while controlling for the other covariate.

Table 4 Estimates (standard errors) for models, gender, dmf and gender + dmf

Parameter	Model gender or dmf	Model gender + dmf
Tooth 14		
β(gender)	−0.0740 (0.0080)	−0.0766 (0.0081)
β(dmf)	−0.0729 (0.0086)	−0.0741 (0.0085)
Tooth 15		
β(gender)	−0.0564 (0.0085)	−0.0594 (0.0087)
β(dmf)	−0.0613 (0.0089)	−0.0628 (0.0090)

The issue of the robustness of the AFT model against the omitted covariates is further illustrated in Table 4. The effect of gender remains almost unchanged in both models gender and gender + dmf and analogous conclusion holds also for the effect of dmf.

5 Conclusions

It has been shown that the emergence processes of teeth 14 and 15 are significantly different between boys and girls and that the caries status of a primary predecessor expressed by the dmf score has a significant effect on the emergence of permanent successors.

Predictive emergence curves have been drawn which can be used for diagnosis and treatment planning in paediatric dentistry. Further, it was found that the acceleration effect of caries on a primary predecessor on the emergence of its successor was stronger for boys than for girls.

Finally, R-scripts used to perform the analysis using the library `smoothSurv` can be found in the downloadable distribution of this library.

6 Discussion

Interval-censored data are not rare in medicine, especially in dentistry, yet they are often not analysed with the proper techniques. Our article tried to give an overview of available approaches in a hope that their use will increase. Unfortunately, the daily use of relevant techniques is still complicated by insufficient ready-to-use software support.

Further, it should be mentioned that Bayesian methods convey many attractive properties useful in the analysis of interval-censored data. Owing to the fact that all unknown quantities are treated in the same manner by Bayesian techniques, one can include (unknown since censored) true event times in the model as additional parameters while focusing the inference only on parameters of interest (e.g., regression parameters). Necessarily, there is no additional complexity when analysing interval-censored data compared to right-censored data. However, the review of Bayesian techniques for the survival analysis would go beyond the scope of this text.

Finally, it is shown how the AFT model with a flexible error distribution estimated using the penalized maximum likelihood could be used for the analysis of the interval-censored data.

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