A Bayesian analysis of multivariate doubly-interval-censored dental data

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SUMMARY

A Bayesian survival analysis is presented to examine the effect of fluoride-intake on the time to caries development of the permanent first molars in children between 7 and 12 years of age using a longitudinal study conducted in Flanders. Three problems needed to be addressed. Firstly, since the emergence time of a tooth and the time it experiences caries were recorded yearly, the time to caries is doubly interval censored. Secondly, due to the setup of the study, many emergence times were left-censored. Thirdly, events on teeth of the same child are dependent. Our Bayesian analysis is a modified version of the intensity model of Häkkänen et al. (2000, Scandinavian Journal of Statistics 27, 577–588). To tackle the problem of the large number of left-censored observations a similar Finnish data set was introduced. Our analysis shows no convincing effect of fluoride-intake on caries development.

Keywords: Bayesian analysis; Intensity models; Multivariate doubly-interval-censored data.

1. RESEARCH QUESTION AND COLLECTED DATA

In this paper, we present a Bayesian analysis of a longitudinal dental data set (the Signal Tandmobiel® study) to tackle the following research question: Does fluoride-intake at a young age have a protective effect on caries in permanent teeth? Our analyses will be limited to the caries experience of the four permanent first molars (teeth number 16, 26, 36, 46 in European dental notation).

In this study, detailed oral health data at tooth and tooth-surface level (caries experience, gingivitis, etc.) from 4468 Flemish schoolchildren (2315 boys and 2153 girls) born in 1989 were collected annually between 1996 and 2001. The children were cluster-sampled from randomly chosen Flemish schools. Two stratification factors, geographical location (five provinces) and educational system (three school systems), were taken into account. Further details on the design of the study can be found in Vanobbergen et al. (2000).

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Our data suggest that the use of fluoride reduces caries experience in primary teeth, see Vanobbergen et al. (2001) and that fluoride-intake delays the emergence of the permanent teeth, see Leroy et al. (2003). The latter result raises the question whether the fluoride-intake only reduces the time at risk or whether it has also a direct protective effect on caries experience.

Unfortunately, fluoride-intake in children cannot be measured accurately. Indeed, fluoride-intake can come from: (1) fluoride supplements (systemic), (2) accidental ingestion of toothpaste or (3) tap water. Further, the intake from these sources can be recorded only crudely. Therefore, it was decided to measure fluoride-intake by the degree of fluorosis on some reference teeth. Fluorosis is the most common side-effect of fluoride-intake and appears as white spots on the enamel of teeth. For this analysis, a child was considered fluoride-positive (covariate \( \text{fluor} = 1 \)) if there were white spots on at least two permanent maxillary incisors during the fourth year of the study or during both the fifth and sixth year of the study.

The prevalence of fluorosis was relatively low (480 children, 10.8%). In our analysis, 480 fluorosis children and 960 randomly selected fluorosis-free children are included. Case-control subsampling was done to reduce computation time. To check that it did not destroy the stratification, we constructed a \( 5 \times 3 \times 2 \) contingency table with factors province, school system and whether the child is in the subsample or not (subsample). A \( p \)-value of 0.13 was obtained for the significance of the interaction of the third factor with the other two using a likelihood-ratio test in a log-linear model, implying that the stratification is similar in the used and the discarded subsamples.

The prevalence of caries experience at the age of 12 was negligible (at most 1.4%) for all permanent teeth except for the first molars (teeth used in the analysis). For these teeth, the prevalence was 25.8% in children with fluorosis compared to 29.4% in fluorosis-free children, with prevalence of 23.3% and 27.7% for boys, and 27.9% and 31.2% for girls, respectively. Thus, at first sight, the impact of fluoride-intake seems to be minor. However, since the emergence of permanent teeth might be delayed by fluoride-intake, evaluating the impact of fluoride-intake should take into account the time at risk for caries. Hence, in our analysis, the response will be the time between emergence and the onset of caries development. But both tooth emergence and onset of caries development are interval-censored, implying a doubly-interval-censored response. See Figure 1 for a graphical illustration of a possible evolution of a particular tooth.

At the onset of the study, about 86% of the permanent first molars had already emerged. The severity of this censoring will affect the efficiency with which the effect of fluoride-intake can be estimated. We tried two strategies to improve the efficiency of our estimation procedure. First, we included in our analysis the
Table 1. Naive Proportional Hazards Models. Hazard ratios (95% confidence intervals (CI)) between a fluorosis and fluorosis-free group of children while controlling for gender and jaw

<table>
<thead>
<tr>
<th>Group</th>
<th>Model WITHOUT frailties</th>
<th>Model WITH frailties</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>95% CI</td>
</tr>
<tr>
<td>Boys, maxilla</td>
<td>0.787 (0.541, 1.032)</td>
<td>0.704 (0.204, 1.204)</td>
</tr>
<tr>
<td>Boys, mandible</td>
<td>0.733 (0.532, 0.934)</td>
<td>0.613 (0.231, 0.995)</td>
</tr>
<tr>
<td>Girls, maxilla</td>
<td>0.871 (0.698, 1.044)</td>
<td>0.892 (0.610, 1.174)</td>
</tr>
<tr>
<td>Girls, mandible</td>
<td>0.812 (0.670, 0.953)</td>
<td>0.776 (0.559, 0.993)</td>
</tr>
</tbody>
</table>

emergence times of teeth 14, 24, 34, 44, 12, 22, 33, 43 all of which had emerged in more than 60% of cases during the course of the study. By incorporating information on these teeth and using the association between teeth of the same subject (via the concept of ‘the birth time of dentition’, see next section), it was attempted to estimate the true emergence time of the permanent first molars better. Second, emergence times from a Finnish longitudinal data set (Virtanen, 2001), involving 235 boys and 223 girls born in 1980–81 with follow-up from 6 to 18 years, were added to our Flemish data. For these Finnish data, almost all 28 permanent teeth emerged during the study period.

Our research question is not uncommon in dentistry but cannot be addressed within any classical statistical package. For our analysis, we have used the software package BITe (Härkänen, 2003), based on a non-parametric Bayesian survival model developed by Härkänen et al. (2000).

Section 2 presents a frequentist Cox proportional hazards (PH) regression model using the midpoints of the observed intervals as if they were exact observations, to compare our Bayesian model to a more commonly used approach. In the third section, the Bayesian model suggested by Härkänen et al. (2000) and modified for our purposes is explained. Results are presented in Section 4. Section 5 is a discussion of our methods.

2. PROPORTIONAL HAZARDS MODELS USING MIDPOINTS

A standard frequentist Cox proportional hazards (PH) model (Cox, 1972) could be applied, replacing interval-censored observations by the midpoints of the observed intervals and treating the resulting data as right-censored observations. In this way, we analyzed time to caries development for the four permanent first molars. For our analysis, the left-censored emergence times were first assumed to be interval-censored with a lower limit for emergence of 5 years, which is practically the youngest age for the emergence of these teeth (Nanda, 1960). Possible dependencies between the four teeth of the same child can be taken into account, for example by inclusion of a Gamma-distributed frailty component in the model (see Hougaard, 2000).

Based on preliminary Bayesian modelling, we do not distinguish between opposite teeth in the same jaw (horizontal symmetry). However, we do make a distinction between maxillary (upper) and mandibular (lower) teeth and also between teeth in different positions (of a quadrant) in the mouth.

For comparison purposes, we present the same PH model as the one shown here but analyzed by Bayesian methods. Hence, the hazard for the time to caries of the \( j \)th tooth of the \( i \)th child depends on the tooth position, fluor and gender of the child (0 = boy, 1 = girl). More specifically,

\[
\lambda(t|\text{tooth}_j, \text{gender}_i, \text{fluor}_i) = \lambda_0(t) \cdot Z_i \cdot \exp(\beta^T x_{ij}),
\]

\( i = 1, \ldots, N, \ j = 16, 26, 36, 46 \), where \( \lambda_0(t) \) is an unspecified baseline hazard function, \( \beta = (\beta_1, \ldots, \beta_5)^T \), and \( x_{ij} = (\text{fluor}_i, \text{gender}_i, \text{tooth}_j, \text{fluor}_i \times \text{gender}_i, \text{fluor}_i \times \text{tooth}_j)^T \). The covariate ‘tooth’ is a dummy variable that distinguishes teeth in different positions in the mouth (apart from
horizontal symmetry). The term $Z_i$ is either one, corresponding to a model without frailties or a Gamma-distributed frailty term.

Estimates of hazard ratios between the fluorosis and fluorosis-free group controlling for gender and jaw are shown in Table 1. As seen, incorrectly ignoring dependencies between the responses of one child by using a model without frailties artificially decreases the size of the confidence interval. Although both models conclude that the effect of fluorosis on the development of caries on the permanent first molars is at the borderline of 5% significance (Table 1), the results are not reliable. Law and Brookmeyer (1992) have pointed out that the statistical properties of midpoint imputation depend strongly on the underlying distribution of the event times. For that reason, a more sophisticated analysis is needed.

3. The Bayesian survival model for interval-censored data

The non-parametric Bayesian intensity model of Härkänen et al. (2000) provides a flexible tool for analyzing multivariate survival data. Further, a software package written in C, called BITE (downloadable from http://www.rni.helsinki.fi/~tth together with scripts used to perform all analyses presented here), makes the analysis feasible in practice.

3.1 Model for emergence

Let $a_{ij}$ be the (unknown) age at which tooth $j$ of child $i$ emerged. The hazard for emergence at time $t$ is

$$
\lambda^{(e)}_{ij}(t) = f(t - \eta_i|\text{tooth}_j, \text{gender}_i) \times I[\eta_i < t \leq a_{ij}].
$$

(2)

The dependence between emergence times of one child is accounted for by using a subject-specific variable $\eta_i$ called birth time of dentition. This is a latent variable which represents the common time marking the onset of the tooth eruption process and hereby ‘explains’ the positive correlation between eruption times $a_{ij}$ within a subject. Note that $\eta_i$ is practically always less than the first emergence time of the permanent teeth. The intensity of emergence for a particular child is zero before that time, expressed by the indicator $I[\eta_i < t \leq a_{ij}]$. The hazard function $f(\cdot|\text{tooth}_j, \text{gender}_i)$ is defined as piece-wise constant for estimation purposes.

3.2 Model for caries experience

Let $b_{ij}$ be the age at which the $j$th tooth of child $i$ developed caries. The hazard for the caries process is given by

$$
\lambda^{(c)}_{ij}(t) = Z_i \times h(t - a_{ij}|\text{tooth}_j, \text{gender}_i, \text{fluor}_i) \times I[a_{ij} < t \leq b_{ij}],
$$

(3)

where the variable $Z_i$ is an unknown subject-specific frailty coefficient modulating the hazard function. Again, we assume in (3) that $h$ is piece-wise constant. We call the difference $b_{ij} - a_{ij}$ the caries experience-free time.

The covariate ‘fluor’ will be used in two ways. First, for each combination of values of $\text{fluor}$, $\text{gender}$ and $\text{tooth}$, a piece-wise constant hazard function is specified and fitted. Second, the term $h(\cdot|\text{tooth}_j, \text{gender}_i, \text{fluor}_i)$ in (3) is replaced by $h(\cdot) \times \exp(\beta^T x_{ij})$, with $\beta$ and $x_{ij}$ being the same as in (1), thus assuming a PH model for caries experience whilst retaining a piece-wise constant baseline hazard function $h(\cdot)$. 

3.3 Remarks

Our statistical model will involve the above two measurement models. Hence, the possible dependencies among times of interest are taken into account by involving two types of subject-specific parameters, $\eta_i$ and $Z_i$. The first subject-specific parameter $\eta_i$ is included in the model for the emergence and will shift the hazard function in time, whereas the frailty $Z_i$ recognizes that the teeth of one child can be more sensitive to caries than the corresponding teeth of another child, reflecting different dietary behavior, brushing habits, etc.

3.4 Priors for baseline hazard functions

In BITE, the working assumption is that hazard functions are piece-wise constant. Further, for the emergence hazard functions $f(\cdot|\text{tooth}_j, \text{gender}_i)$, the first level of the piece-wise constant and the increment levels are assigned Gamma prior distributions. This will ensure a priori an increasing hazard function for emergence. In the case of caries experience, the first level of the piece-wise constant hazard function, say $h_0$, is assigned a Gamma prior distribution. Further, the level $h_m$ of the $m$th interval has, conditional on the previous levels $h_0, \ldots, h_{m-1}$, a Gamma($\alpha, \alpha/h_{m-1}$) prior distribution. This gives a priori $E[h_m|h_{m-1}, \ldots, h_0] = h_{m-1}$ and ensures that there is no built-in prior assumption of trend in the hazard rate. Finally, the prior for the jump points of each piece-wise constant function is a homogeneous Poisson process, as suggested by Arjas and Gasbarra (1994). Because jump points are assumed to be random and not fixed, the posterior predictive hazard functions will be smooth, rather than piece-wise constant.

3.5 Priors for the random effect terms

The prior distribution for the birth time of dentition $\eta_i$ illustrates how we have combined the Flemish data and the Finnish data and how the timing of emergence of the Finnish data is included in our analysis. We assume that the shapes of the emergence hazard functions $f$ for Finland and Flanders are the same but we do allow for a shift in emergence times by assuming different means for the birth time of dentition in the two countries. More precisely, the prior distribution of $\eta_i$ is assumed normal $N(\xi_0, \tau^{-2})$ for a Finnish child and normal $N(\xi_1, \tau^{-2})$ for a Flemish child. The Bayesian approach allows us to include the dentist’s knowledge on the problem at hand by assigning to the parameters $\xi_0$ and $\xi_1$ independent normal prior distributions with mean 5.2 years and standard deviation 1 year. Both the normal distribution as well as the choice of the prior means and standard deviation of the hyperparameters $\xi_0$ and $\xi_1$ are motivated by the results found in the literature on the earliest emergence of permanent teeth (see Nanda, 1960 or, more recently, Parner et al., 2001). This reflects the dentist’s belief that permanent teeth, on average, emerge slightly after 5 years of age. The parameter $\tau^2$ is assigned a Gamma(2, 2) prior distribution.

The individual frailties $Z_i$ in the model for caries are a priori assumed to be conditional on the hyperparameter $\phi$, independent and identically Gamma-distributed with both shape and inverse scale equal to that hyper-parameter. The hyper-parameter itself is then given a Gamma(2, 2) prior distribution. Sensitivity of the results with respect to the choice of parameters for priors of hyperparameters $\xi_0, \xi_1, \tau$ and $\phi$ will be discussed in Section 4.

3.6 Treatment of censored data

Left- and interval-censoring are treated by data augmentation (Tanner and Wong, 1987). First, the left-censored emergence times of all teeth are changed into interval-censored emergence times with a lower
limit equal to 4 years, implying that less internal information is used here than previously with the frequentist PH model where the limit was 5 years. In the case that both emergence and caries development were observed within one observational interval, we force sampled values of the Markov Chain Monte Carlo (MCMC) to satisfy \( b_{ij} > a_{ij} \).

### 3.7 Bayes inference on model components

The posterior distributions based on the model with prior assumptions described in the previous paragraphs are minor modifications of those derived in Härkänen et al. (2000). Our Bayesian model is complex and requires the use of MCMC sampling techniques (Gilks et al., 1996). The software package BITE (Härkänen, 2003), based on the Metropolis–Hastings algorithm (Metropolis et al., 1953; Hastings, 1970), was used to sample from the posterior distributions. Further, BITE employs the reversible jump approach of Green (1995) to sample piece-wise constant hazard functions. We carried out two runs, each with 20,000 iterations of burn-in followed by 14,000 iterations with a 1:4 thinning to obtain a sample from the posterior distribution. We used the Gelman and Rubin (1992) test to check for convergence.

### 4. RESULTS

#### 4.1 A non-parametric model with Flemish and Finnish data

To evaluate the effect of fluoride-intake on the development of caries on the permanent first molars, we have calculated the posterior expectations of hazard ratios \( h(t|\text{tooth, gender, fluorosis})/h(t|\text{tooth, gender, fluorosis-free}) \). These hazard ratios together with their 95% equal-tail point-wise credibility intervals can be found in Figure 2. The PH assumption with respect to covariate fluor seems to be satisfied since credibility intervals in all cases cover a horizontal line. In three cases, this horizontal line is close to the dotted–dashed line \( y = 1 \) implying no effect of fluoride-intake on caries development. A positive effect of fluoride-intake seems to be present only for mandibular permanent first molars in boys. There are also no deviations from the PH assumption with respect to gender and tooth (plots are not shown). This allowed us to assume for the caries model a PH effect of the three covariates, possibly including some interaction terms. By this semi-parametric assumption, it was hoped to see more clearly the effect of fluoride-intake on caries experience.

#### 4.2 A proportional hazards model with Flemish and Finnish data

For the reasons stated in the previous paragraph, we have fitted a model where the caries hazard function (3) was changed into

\[
\lambda_{ij}^{(c)}(t) = Z_i \times h(t) \times \exp(\beta^T x_{ij}) \times I[a_{ij} < t \leq b_{ij}],
\]

where \( x_{ij} \) and \( \beta \) are same as in (1). The additional \( \beta \)-parameters were given an \( N(0, 10^2) \) prior. However, the hazard function for emergence is still defined by (2). Posterior expectations of the hazard ratios between the fluorosis groups while controlling for the other covariates are given in the left-hand part of Table 2.

The PH analysis for caries gives similar conclusions to the previous non-parametric analysis. A positive effect of fluoride-intake is now seen for the mandibular permanent first molars of boys and has a borderline positive effect for the maxillary permanent first molars of boys. However, no effect of fluoride-intake was seen for girls.
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Fig. 2. Bayesian Non-Parametric Model based on Flemish and Finnish Data. Posterior means of the hazard ratios between the fluorosis groups (solid curve), 95% point-wise equal-tail probability region (dashes).

Table 2. Bayesian Proportional Hazards Models. Hazard ratios (95% equal-tail credibility intervals (CI)) between fluorosis groups while controlling for gender and jaw for models fitted using both Flemish and Finnish data and Flemish data only

<table>
<thead>
<tr>
<th>Group</th>
<th>Flemish and Finnish data</th>
<th>Flemish data only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poster. mean</td>
<td>95% CI</td>
</tr>
<tr>
<td>Boys, maxilla</td>
<td>0.674</td>
<td>(0.492, 1.010)</td>
</tr>
<tr>
<td>Boys, mandible</td>
<td>0.572</td>
<td>(0.414, 0.850)</td>
</tr>
<tr>
<td>Girls, maxilla</td>
<td>0.991</td>
<td>(0.721, 1.364)</td>
</tr>
<tr>
<td>Girls, mandible</td>
<td>0.840</td>
<td>(0.608, 1.136)</td>
</tr>
</tbody>
</table>

Remark concerning hyperparameters

The posterior expectations and 95% equal-tail credibility intervals of the hyperparameters related to the birth times of dentition $\eta_i$ and frailties $Z_i$ are given in the upper part of Table 3. The non-parametric model and PH model for caries give similar results.

We now state our conclusions concerning the emergence process in Flanders and Finland. The emergence process starts slightly earlier in Finland (by approx. 0.2 years) than in Flanders, as is seen by the difference in the posterior expectations of the means of birth time of dentition. The MCMC output for the hyperparameters can also be used to estimate properties of the predictive distributions of birth time.
Table 3. Bayesian Models with Flemish and Finnish Data. Posterior means and 95% equal-tail credibility intervals for the hyperparameters: $\mu_0$, conditional expectation of $\eta_i$ for Finland; $\mu_1$, conditional expectation of $\eta_i$ for Flanders; $\tau^{-2}$, conditional variance of $\eta_i$; $\phi^{-1}$, conditional variance of frailties $Z_i$ (top of the Table). Means of the posterior predictive distributions and 95% equal-tail posterior predictive intervals for the birth time of dentition $\eta_i$ in Finland and Flanders, respectively, and for the frailty term $Z_i$ (bottom of the table)

<table>
<thead>
<tr>
<th>Hyperparameter</th>
<th>Non-parametric model</th>
<th>Cox regression model</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_0$</td>
<td>5.47 (5.40, 5.54)</td>
<td>5.45 (5.38, 5.52)</td>
</tr>
<tr>
<td>$\mu_1$</td>
<td>5.69 (5.64, 5.73)</td>
<td>5.68 (5.64, 5.73)</td>
</tr>
<tr>
<td>$\tau^{-2}$</td>
<td>0.48 (0.45, 0.52)</td>
<td>0.49 (0.45, 0.52)</td>
</tr>
<tr>
<td>$\phi^{-1}$</td>
<td>3.85 (3.57, 4.17)</td>
<td>3.94 (3.58, 4.28)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-parametric model</th>
<th>Cox regression model</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\eta_i$ (Finland)</td>
<td>5.48 (4.12, 6.79)</td>
<td>5.45 (4.05, 6.84)</td>
</tr>
<tr>
<td>$\eta_i$ (Flanders)</td>
<td>5.69 (4.33, 7.09)</td>
<td>5.69 (4.34, 7.01)</td>
</tr>
<tr>
<td>$Z_i$</td>
<td>1.02 (10^{-6}, 6.90)</td>
<td>0.95 (10^{-6}, 6.45)</td>
</tr>
</tbody>
</table>

of dentition and frailties. Their means and 95% equal-tail posterior predictive intervals are shown in the bottom part of Table 3, which shows that the average of Finnish birth time of dentition is close to 5.5 years of age, slightly higher than the prior expectation but close to the value obtained by Häkänen et al. (2000) on another Finnish data set. The 95% posterior predictive intervals show that the actual moment of birth time of dentition varies between about 4 and 7 years of age. Finally, the 95% posterior predictive interval of $Z_i$ shows a clear heterogeneity in the frailty for caries experience.

4.4 Sensitivity analysis

First, model (4) was fitted using Flemish data only, to see how influential the inclusion of the Finnish data was. As seen in Table 2, the hazard ratios changed only slightly. The same was true for the remaining parameters. Moreover, the Finnish data improved only slightly the precision with which the emergence of the first permanent molars was estimated.

To see how the behavior of the parameter estimates changes when informative priors for the hyperparameters are modified, we have fitted the proportional hazards model with Flemish data only, using different choices of priors for the hyperparameters. Specifically, we used normal distributions $N(3, 2)$, $N(4, 1)$, $N(5.2, 1)$, $N(6, 1)$ as priors for the expectation $\xi_0$ of birth time of dentition $\eta_i$. The standard deviation of the normal prior with mean 3 years was increased so as to cover realistic emergence times of permanent teeth. We used Gamma(0.1, 0.1), Gamma(2, 2) and Gamma(10, 10) distributions as priors for the precision $\tau$ of the variance of the birth time of dentition and for the precision $\phi$ of frailties $Z_i$. All other parameters were given flat priors and there is, thus, no reason to modify them.

Posterior means and 95% equal-tail credibility intervals for hazard ratios between the fluorosis and fluorosis-free groups for different choices of the prior distributions are shown in Figure 3, which shows that the influence of the choice of the prior distribution is not strong.

We argue that our other assumptions are not strong. Indeed, we only assume that the distributions of the birth time of dentition differ between Finnish and Flemish populations only in their means. Moreover, as indicated earlier, the Finnish data had only a slight impact on the results for the Flemish data. Further,
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the baseline hazards were estimated non-parametrically. Finally, different choices for the priors of the hyperparameters led to similar results as previously discussed.

5. DISCUSSION

The model presented here allows for the analysis of survival data in dental research where interval-censored data and dependencies between observations (e.g. between teeth in the same mouth) are common. Our specific application is to a typical dental research question, i.e. whether fluoride-intake has a protective effect for caries. The results show that the protective effect of fluoride-ingestion is not convincing. We observed a positive effect only for mandibular teeth of boys. This agrees with current guidelines for the use of fluoride in caries prevention, where only the topical application (e.g. fluoride in tooth paste) is considered to be essential (Oulis et al., 2000).

We acknowledge that our analyses could have been more refined if the amount of left- and right-censoring was less, for instance if the study had started approximately one year earlier and ended in high school. This would make our analyses less dependent on prior assumptions. Yet these prior assumptions are simply a reflection of basic dental knowledge and it would be a waste not to use them. Moreover, to our knowledge, the Signal Tandmobiel® trial is possibly the largest longitudinal study executed with such great detail on dental aspects.
This paper has illustrated the usefulness of our Bayesian approach, i.e. the possibility to incorporate prior information and to relax the parametric assumptions often made in survival analysis with interval-censored data. However, our approach is computationally demanding. On a Pentium IV 2 GHz PC with 512 MB RAM, one BITE run took about 5 days to converge. However, in an epidemiological analysis where there is correlation among the subjects, where the response and/or the covariates are (right-, left- or interval-) censored and when we wish to avoid parametric assumptions, we doubt any classical approach will suffice. Furthermore, the BITE package of Häkänen (2003) gave us the possibility to avoid the specification of a parametric model. We, therefore, would recommend this package for hard problems in survival analysis.

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