Truncated Recurrent Event Survival Models for Methadone Data

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SUMMARY

Truncated multivariate survival models are proposed for the analysis of data from the South Australian Methadone Program. Injecting drug users may have several entries to and exits from the program. A marginal approach for recurrent events is found to provide a useful and simplified basis for modelling the retention of injecting drug users on methadone. The likelihoods and results of fitting two forms of truncated survival models are presented, together with recommendations for statistical analysis using S-PLUS. The relative merits of the marginal approach, in this context, and alternative ways of viewing the data are discussed.

Key words: multivariate survival models; recurrent events; truncation; methadone; injecting drug user; S-PLUS.

1. Introduction

Survival analysis has profoundly influenced biomedical research and applied statistics over the past two decades. This field of statistics involves the study of survival times for a group or groups of individuals, for whom survival time is defined from a well-defined initiating event, to a predefined outcome event or 'failure' for each individual. Interest focusses on the distribution of these times and the effect on survival of any explanatory variables. Analysis is often complicated by incomplete, or censored observations, i.e., the failure event may not have been observed for all individuals at the conclusion of follow-up. In many studies, one type of event or failure is of interest, such as death following a diagnosis of AIDS or cancer, or the development of AIDS following a positive HIV antibody test.

Modern survival analysis dates from the path-breaking work of Cox (1972, 1975) on the proportional hazards model, which laid down a sound theoretical basis for analysis. The literature has since grown enormously, with major advances in both the asymptotic and counting process frameworks. The classical texts are Kalbfleisch & Prentice (1980) and Cox & Oakes (1984) which treat the topic primarily from the asymptotic approach. More recently, the texts by Andersen, Borgan, Gill & Keiding (1993) and Fleming & Harrington (1991) provide useful accounts of the counting process approach. Excellent overviews of recent developments in the field are also to be found in Clayton (1988, 1994), Klein & Goel (1992), Lin (1994) and Kooperberg, Stone & Truong (1995).

Recently, we have been concerned with analysing data from the South Australian Methadone Program observed over the decade 1981-1991. In particular, we have data on 269 injecting drug users who entered the program at least once during this period. If an individual was not seen for a break of two or more weeks, this defined the end of that program. 113 individuals returned for a second or subsequent program, and of these, 45 entered a third program. We are interested in factors associated with retention on methadone and patterns of individual entries to and exits from subsequent programs.

The data arising from this study may be modelled by multivariate failure time methods, or more particularly, methods for recurrent events. Such data are encountered when each subject under study may experience more than one event or failure; here the events are of the same type. The analysis of multivariate failure time data has a recent substantial history and an on-going debate as to the appropriate way to analyse such data. Clayton (1994) provides an interesting overview of the development of methods based on two streams of overlapping thought, namely Cox's regression model for life tables (1972) and Nelder & Wedderburn's formulation for generalised linear models (1972). Our interest here lies in the former approach, in particular Cox's proportional hazards regression model. We may, very loosely, treat the individual patterns of entries to and exists from the methadone program as a form of 'filtering' (Andersen et al, 1993), where times on the program coincide with treatment.

Since individual injecting drug users may have repeated programs, we need to consider subject-level effects which may induce correlation between recurrence times. Frailty models (Clayton, 1988, 1994) can account for heterogeneity between subjects by specifying an appropriate parametric distribution for a so-called frailty variable. A less complex option, which we pursue here, is to model this dependence directly through the covariates, which is particularly appropriate if there is evidence of independence between repeated failure times for each individual. One may also view the methadone survival data as the sum of two types of survival times : times 'on' and ‘off’ methadone; or indeed as longitudinal data with two states. However, we demonstrate in this paper that a marginal approach (see for instance Lin, 1994) to the recurrent event survival data, using truncated survival models, is realistic and appropriate for studying retention on the South Australian Methadone Program.

We begin Section 2 by discussing survival models for recurrent events within the context of the methadone study. Two truncated survival models are proposed, both addressing questions of interest about retention on methadone. We consider a likelihood-based marginal approach within the Andersen & Gill (1982) framework, and the appropriate partial likelihoods for both models proposed are presented. A brief summary of our exploratory analyses leads the way in Section 3, with notes on how the final models were obtained. We present the discussion in Section 4, with a note on the results and comments on alternative approaches. S-PLUS commands for implementing the models are set out in the Appendix.

2. Survival models for recurrent events

A general definition of survival time for recurrent events is not easy to obtain as it may take many forms, depending on the context. For the marginal approach, survival time (T_{ik}), is defined as the time from entry to the study up until the k^{th} recurrence for the i^{th} subject ($i = 1, ..., n, k = 1, ..., K$), where there are K types of failures in the multivariate case or at most K recurrences of the same failure type.

Within the proportional hazards framework, we are able to derive the marginal distribution for each failure type such that the hazard for the i^{th} individual for the k^{th} failure type is

$$\lambda_k(t) = \lambda_0(t)e^{\beta' Z_{ik}(t)} \tag{1}$$

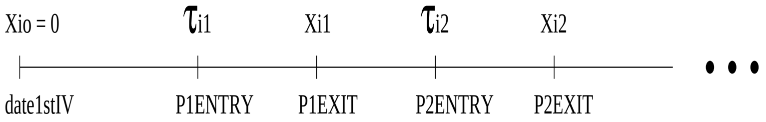
or

$$\lambda_k(t) = \lambda_{0k}(t)e^{\beta' Z_{ik}(t)} \tag{2}$$

depending upon whether we assume the baseline hazards are the same or different (respectively) over the K failure types. $\lambda_0(t)$ and $\lambda_{0k}(t)$ are the baseline hazard functions, $\boldsymbol{Z}_{ik}(t)$ is the covariate vector for the i^{th} individual on the k^{th} program at time t, and $\boldsymbol{\beta}$ is the corresponding vector of regression parameters. We note here that $\boldsymbol{\beta}$ is taken to be the same amongst the marginal models, an assumption justified by introducing appropriate type-specific covariates if necessary.

Assuming that observations within each failure type are independent, partial likelihood functions for models (1) & (2) can be readily obtained. Then, one may redefine the definition of survival time and/or the risk-set indicators $Y_{ik}(t)$ in order to reflect the nature of the problem at hand (see Lin, 1994).

For the methadone data, the failure event is defined as an exit from the program. A typical case may take the following form:



where $X_{ik} = \min(T_{ik}, C_{ik})$, $\mathcal{T}_{ik}$ = calendar time at entry to the k^{th} program for the i^{th} individual, and C_{ik} = censored survival time for individual i on the k^{th} program; date1stIV is the calendar time of first injecting drug use.

We focus on the modelling of two different definitions of survival time, both *truncated*, since in each case individuals come under observation only after a certain time since the time origin, here defined to be the date at first injecting drug use. Incorporating truncation effects is a natural way to condition upon the fact that each individual has to have been a user and/or under observation and potentially able to enter a particular program.

Our first approach (model A) is based upon T_{ik} being (for the the i^{th} individual) the time from date of first injecting drug use to exit from program k (i.e. X_{ik}). The truncation times ($\mathcal{T}_{ik}$) are defined from date at first injecting drug use up until entry to program k. For the second approach (model B) we define T_{ik} to be the time from exit from the last program ($k-1$), to the exit time from program k (i.e. $X_{ik} - X_{i,k-1}$), where $X_{i0} = 0$. Here, the truncation time is defined as the time from the exit from program $k-1$, up to the entry to program k.

Assuming that the hazards remain constant over programs, the partial likelihood for model A is :

$$\mathcal{L}_P(\boldsymbol{\beta}) = \prod_{i=1}^{n} \prod_{k=1}^{K} \left\{ \frac{\exp\{\boldsymbol{\beta}' Z_{ik}(X_{ik})\}}{\sum_{j=1}^{n} \sum_{l=1}^{K} Y_{jl}(X_{ik}) \exp\{\boldsymbol{\beta}' Z_{jl}(X_{ik})\}} \right\}^{\Delta_{ik}} \tag{3}$$

where $\Delta_{ik} = I(T_{ik} \leq C_{ik})$ and

$$Y_{jl}(X_{ik}) = \begin{cases} 1 & \mathcal{T}_{jl} < X_{ik} \leq X_{jl} \\ 0 & \text{otherwise} \end{cases} .$$

The log partial likelihood is then

$$L_P(\boldsymbol{\beta}) = \sum_{i=1}^{n} \sum_{k=1}^{K} \Delta_{ik} \left\{ \boldsymbol{\beta}' Z_{ik}(X_{ik}) - \log \left[\sum_{j=1}^{n} \sum_{l=1}^{K} Y_{jl}(X_{ik}) \exp\{\boldsymbol{\beta}' Z_{jl}(X_{ik})\} \right] \right\} . \tag{4}$$

(4) is modified for model B by replacing X_{ik} in (3) with $(X_{ik} - X_{i,k-1})$ and defining the risk set indicator to be

$$Y_{jl}(X_{ik} - X_{i,k-1}) = \begin{cases} 1 & \mathcal{T}jl - X_{j,l-1} < X_{ik} - X_{i,k-1} \leq X_{jl} - X_{j,l-1} \\ 0 & \text{otherwise} \quad . \end{cases}$$

We can model hazards that differ for an individual's first, second and third treatment program (i.e. (2)) with the partial likelihood for model A then being

$$\mathcal{L}_P(\boldsymbol{\beta}) = \prod_{i=1}^{n} \prod_{k=1}^{K} \left\{ \frac{\exp\{\boldsymbol{\beta}' Z_{ik}(X_{ik})\}}{\sum_{j=1}^{n} Y_{jk}(X_{ik}) \exp\{\boldsymbol{\beta}' Z_{jk}(X_{ik})\}} \right\}^{\Delta_{ik}} ,$$

where

$$Y_{jk}(X_{ik}) = \begin{cases} 1 & \mathcal{T}jk < X_{ik} \leq X_{jk} \\ 0 & \text{otherwise} \quad . \end{cases}$$

The corresponding log of the partial likelihood is then :

$$L_P(\boldsymbol{\beta}) = \sum_{i=1}^{n} \sum_{k=1}^{K} \Delta_{ik} \left\{ \boldsymbol{\beta}' Z_{ik}(X_{ik}) - \log \left[\sum_{j=1}^{n} Y_{jk}(X_{ik}) \exp\{\boldsymbol{\beta}' Z_{jk}(X_{ik})\} \right] \right\} ,$$

with the previously described modifications again relevant for model B.

In general, estimates of the standard error of $\hat{\boldsymbol{\beta}}$ may be biased by assuming marginal-type models for analysis in the presence of dependence (i.e repeated programs within individuals) in the data. Robust covariance estimators of $\hat{\boldsymbol{\beta}}$ are available (see Wei, Lin & Weissfeld, 1989) and are readily fit in S-PLUS for the truncated models considered here.

We note that individuals who have an incomplete observation on the k^{th} program have no data on the $k+1^{th}$ or any subsequent programs; in each case, this is due to the end of follow-up. In our study, incomplete observation on subsequent programs depends on the length of time spent on previous programs, inducing data that is not missing completely at random (see Rubin & Little, 1987). Moreover, we observe a trend towards increased retention on methadone over the decade. We establish however (see Section 3) that the missingness may be regarded as 'missing at random', where the observed effects are effectively captured by appropriate choice of the covariates.

3. Retention on the South Australian Methadone Program

Methadone is widely regarded as an effective oral opiate substitute for heroin, and the South Australian Methadone Program has operated from one site in Adelaide since 1981. 229 of the 269 individuals in the present study were randomly sampled from the 1,239 who enrolled in the program between 1 January 1981 and 30 June 1991; the remaining 40 individuals were all known HIV-positive injecting drug users who had entered the program at least once over the decade. The available information included many covariates describing basic demographic variables such as age and sex, variables describing drug-related and treatment history, social-demographic variables including employment and marital status, sexual preference and several clinical and biochemical covariates. Individuals participated in at most three consecutive programs i.e. they re-entered the South Australian Methadone Program up to three times. Less than 50% of the 269 injecting drug users entered more than one program and 17% entered three or more.

3.1 Prevalent and incident univariate survival models

The three consecutive programs were analysed separately in the first instance using incident (where time origin is date of first injecting drug use) and prevalent (where the time origin is date of entry to the program) models. For discussions of such survival models, see Wang, Brookmeyer & Jewell (1993) and Ripley & Solomon (1995). A complication here is that data on date of first injecting drug use were missing for 39 individuals. Using Buck's method (see Rubin & Little, 1987, pp. 44-47) and regressing date1stIV on *sex* and *age* for the other 239 individuals, the 39 missing values were imputed. The imputed values were very similar in distribution to the non-missing values.

Each survival regression was performed in two stages where a best-fitting model of entry characteristics was found, followed by a best-fitting model including program covariates. The purpose of the two-stages was to maintain the 'order' of the variables and how they arose. Models were fit in S-PLUS using stepwise regression based on the log partial likelihoods.

Kaplan-Meier estimates of the survival functions for each of the prevalent models (P1 - P3) were plotted (see Figure 1) and suggested little change in the hazards over programs for the first year. This observation was supported by the log-rank test which found no significant differences between the survival curves, although there is some suggestion of non-proportionality.

Table 1 presents the results of our best-fitting incident and prevalent models for the initial program (P1); the resulting estimates are very similar. Being HIV positive (HIV, 1 = yes), Hepatitis C positive (HEPC, 1 =yes), and receiving methadone from a chemist (METHCHEM, 1=yes) were all statistically significantly associated with better retention on the first methadone program. A history of imprisonment (PRISON, 1 = yes), transferring from interstate (TRANSFER, 1 = yes) and a high rate of urine tests positive for opiates (URATEOP, per month) were significantly associated with poorer retention. (A subgroup analysis confirmed the latter was an ordered effect.) Note that PRISON and TRANSFER did not vary from program to program for a given individual, whereas the remaining covariates could do so.

In a similar fashion, we fit prevalent and incident models for P2 and P3, initially with a simplified model containing only entry covariates, plus information from previous programs, as well as those available at entry to P1. However, when we added the program two covariates, few remained significant. Similarly, the addition of program three covariates also resulted in few remaining significant. The results are set out in Tables 2 and 3 respectively.

Having a higher starting dose of methadone (1STDOSE, mg) was significantly associated with retention in the best-fitting prevalent and incident models for the second program. The significance and effect of METHCHEM was maintained in both models, while that for URATEOP was maintained only for the incident model. Trends in the other covariates were similar to those in Table 1, but not statistically significant. METHCHEM is again associated with significantly better retention on the third program. In the incident model, the time from first injecting drug use to P1 entry (GAP1) indicates that longer periods between first injecting drug use and entering the methadone program were associated with poorer retention. As for P2, the effects of the other covariates were similar but not statistically significant.

We note here that maximum dose of methadone was omitted for the purposes of the present analysis. Dosage increased to a maximum before decreasing again, however, the time of maximum dose was not recorded. Moreover, there are difficulties in interpreting the effect of such time-related variables. It is interesting to note that the effects of the other covariates were little altered by excluding maximum dose, although the goodness-of-fit was significantly poorer.

3.2 Analysis of 'gap' times and multivariate truncation models

We examined correlations of the within-individual times spent on programs. All such correlations were typically small, justifying the independence assumption of the marginal approach and the treatment of incomplete observations as missing at random. For the cohort of individuals who completed three consecutive programs (n=26) the correlations between P1 and P2, P2 and P3, and P1 and P3 are respectively 0.23, 0.14 and 0.11. For the cohort who completed two consecutive programs (n=84) the correlation between P1 and P2 is 0.27; however this correlation reduces to 0.18 with the removal of a single individual who spent almost five years on P1 and three years on P2.

It is important to analyse in detail the 'gap times' between programs as they can be considered to represent a different type of time. Kaplan-Meier curves for the times between the date at first injecting drug use and entry to P1 (i.e., GAP1), P1 exit and P2 entry (i.e., GAP2), and P2 exit and P3 entry (i.e., GAP3) were plotted (see Figure 2) and found to have significant differences ($P < 0.05$). Upon inspection, there was an indication that people tended to have smaller gap times as they progressed to subsequent programs, although GAP2 and GAP3 are very similar. Due to the nature of the heterogeneous gap times, it is important that they be accounted for directly in the modelling process, and this justifies the formulation of the two truncated models defined in Section 2.

In order to arrive at the 'best' model for the data for both types of truncation, an important consideration was whether to fit any covariate whose information may change over different programs as program-specific covariates, or as a single covariate representing the effects averaged over programs. Most exploratory fittings suggested no benefit in the use of time-dependent or individual program-specific covariates as effects and significance levels remained relatively consistent over programs.

Regression estimates of covariate effects for our final (reduced) multivariate models for both types of truncation are set out in Tables 4 and 5. We can clearly see that both the magnitude and direction of covariate effects are very similar for models A and B. We retained HIV in model A for comparison with model B.

The naive and robust estimates of standard error are very similar, particularly for model B. The robust standard errors are smaller than the naive standard errors for PRISON under both models and for METHCHEM under model B. Although PRISON does not change over programs within an individual, it is disproportionately represented over programs. The patterns of obtaining methadone from a chemist were quite variable within and between individuals as compared with the other covariates. However, neither the substantive effects nor the goodness-of-fit are significantly changed by fitting METHCHEM as a program-specific covariate.

Overall, these results are consistent with the relatively small observed within-individual correlations and provide further justification of the marginal approach. It is worth noting here that if the marginal models are correct then the naive and robust estimates of standard error are asymptotically equivalent (Lin, 1994).

The year of entry to the methadone program (PENTRY, 1981-1984 is the baseline for comparison) is important in the multivariate models, suggesting a significantly decreased relative risk as we progress from 1981 to 1991. All remaining covariates displayed in Tables 4 and 5 have similar effects to the previously detailed prevalent and incident univariate models. We note here that time to a positive Hepatitis C diagnosis (mean $\approx$ 19 years since date1stIV) was also fitted as a time-dependent covariate, but was not significant. Tables 4 and 5 suggest that the greater the gap between programs (GAPS, days), the poorer the retention on methadone. Due to the heterogeneous nature of the gap times noted above, GAP1, GAP2 and GAP3 were fitted as program-specific covariates. For model A, Table 6 suggests that GAP1 followed by GAP2 contribute most to the overall significance of GAPS. Nonetheless, the observed relative risks suggest relatively consistent effects and similarly for model B. Including the covariates PENTRY and GAPS and incorporating truncation in our models allows us to (indirectly) adjust for observed temporal trends.

A check for non-linearity of the continuous covariates was investigated using martingale residual plots. The plot for gap times for model A is shown in Figure 3, with similar results observed for model B. The approximate linear fit illustrated in Figure 3 provides justification for the use of Cox models A and B.

Finally, stratified models assuming different hazards over programs were also fitted, and covariate effects were found to remain consistent. This finding suggests that for the methadone data, there is no benefit gained by modelling under the assumption of different (as opposed to constant) hazards for each program.

4. Discussion

Models A and B differ according to their definition of survival time. For the i^{th} individual on program k (where $i = 1, ..., 269$ and $k = 1, 2, 3$) survival time begins for model A at date1stIV and for model B at the time of exit from program $k - 1$ (or date1stIV if $k = 1$) and finishes for both models at the exit from program k. Both forms of survival times are then truncated at entry to program k, relative to their starting points.

As noted in Section 2, individuals with an incomplete observation on P1 or P2 have no data for any subsequent programs which consequently violates the assumption of missing completely at random. The proportions of observations censored for P1 and P2 remain close to 25% at 66/269 and 29/113 respectively, with an increase to 19/45 for P3. However, with our large dataset, and with individuals monitored for reasonably long periods over the decade, the consequences of such a violation are likely to be minimal. Moreover, we have shown that missing at random is a reasonable assumption for the methadone data, where any dependence may be captured by appropriate modelling of the covariates.

Working as we are within the semi-parametric framework there is no need to specify the underlying hazard in our modelling. However, if we had some knowledge as to the nature of these hazards and were able to classify them as taking a particular form, then it may be possible to work within a parametric framework. Complementary log-log transforms were plotted for each of the three programs and suggested the hazards were monotone decreasing except in the tails where the Weibull assumption underestimates survival (although there is much less information available there anyway). One possibility we are currently considering is to model the data using a multivariate Weibull distribution (Johnson & Kotz, 1972). However, while a parametric framework for analysis of univariate failure time data may be well understood, the multivariate equivalent is likely to be analytically and computationally complex, and may not simplify matters.

In conclusion, the marginal approach with truncated survival times appears appropriate for the analysis of these data, with consistency obtained for the two types of truncation defined by models A and B. Nevertheless, it would be interesting to study the alternative approaches outlined in the introduction, as each may shed new light on the methadone data.

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APPENDIX

Fitting multivariate survival models in S-PLUS

An important development in modern survival analysis has been the representation of the Cox model in the counting process framework of Andersen & Gill (1982). One motivation for using the counting process approach lies in the complexity involved with deriving large sample asymptotic properties of $\hat{\boldsymbol{\beta}}$ within the partial likelihood framework for more complex survival models. The counting process approach is able to cope with complicated censoring patterns, truncated data, and time-dependent covariates relatively simply, and is readily implemented within S-PLUS as well as SAS. We performed the data analysis in S-PLUS 3.3 (see Therneau, 1994).

Observations consist of rows of data which contain covariate values $\boldsymbol{Z}$, a censoring indicator (where 1 = failure event, 0 = censored) and a time interval (Start, Stop] within which this information applies. A stratum indicator is also necessary if we assume that hazards are different over strata.

A typical display of such information is illustrated below for an injecting drug user entering the program 2556 days after the date of first injecting drug use (i.e. date1stIV). After 184 days, they left the program and then re-entered 274 days later. This stay lasted 123 days; they then left for a further 789 days, at which point they re-entered for a third time. Time on the third program was censored after 77 days due to the end of the observation period, 31st June 1991. The truncation for model A is accounted for through the following set-up of 'Start's and 'Stop's (recall that all entries are relative to the time origin date1stIV):

Start	Stop	Cens	Sex	First Dose
2556	2740	1	F	20
3014	3137	1	F	20
3926	4003	0	F	85

Under model B, the 'Start' and 'Stop' entries are relative to the exit from the previous program, or date1stIV if no previous program:

Start	Stop	Cens	Sex	First Dose
2556	2740	1	F	20
274	397	1	F	20
789	866	0	F	85

Including covariates that may change over time requires an extended set-up of the data in S-PLUS. For illustration, we consider the time-dependent 'Hepatitis C status' covariate for the above individual, who was known to contract Hepatitis C 30 days after entering the program for the third time. Here, time on the program is split into two parts :

Start	Stop	Cens	Sex	First Dose	HepCstatus
2556	2740	1	F	20	0
3014	3137	1	F	20	0
3926	3956	0	F	85	0
3956	4003	0	F	85	1

Assuming constant hazards over programs, we may fit model (1) using a command of the form :

```
cox.eq<- coxph(Surv(Start,Stop,Cens) ~ z1 + ··· + zp, data = meth)
```

where Start(k) is the time at which program k begins and Stop(k) is the time at which an individual is censored or leaves program k. Then Start = (Start(1), Start(2), ... , Start($k-1$), Start(k)) and similarly for Stop and Cens.

The definition of covariates whose values may change over k programs depends upon whether separate covariates for each program or a single covariate representing the (average) effect over all programs are appropriate. Average covariate vectors can be set up like the illustrated 'Start' vector. Alternatively for the case of program specific covariates, covariate values may be set at zero, other than those detailing the program they are representing. We note that covariate values set at zero may in fact be set to other values if the marginal assumption does not hold and conditioning upon previous event histories is required.

Assuming hazards are different over programs (i.e model (2)), we stratify by programs using the stratum indicator $\boldsymbol{Z}_{p+1}$ say. The S-PLUS command then takes the form :

```
cox.diff<- coxph(Surv(Start,Stop,Cens) ~ z1 + ··· + zp + strata(zp+1), data = meth)
```

with Start, Stop and Cens taking on the same forms described above as appropriate for model (1). One can also use interaction terms, e.g., $(z_1 + z_2) *$ `strata(program)` within the S-PLUS code.

Finally, robust covariance estimates are simply obtained by the subcommand '`cluster(id)`', where this asserts that subjects with the same value of the variable '`id`' may be correlated.

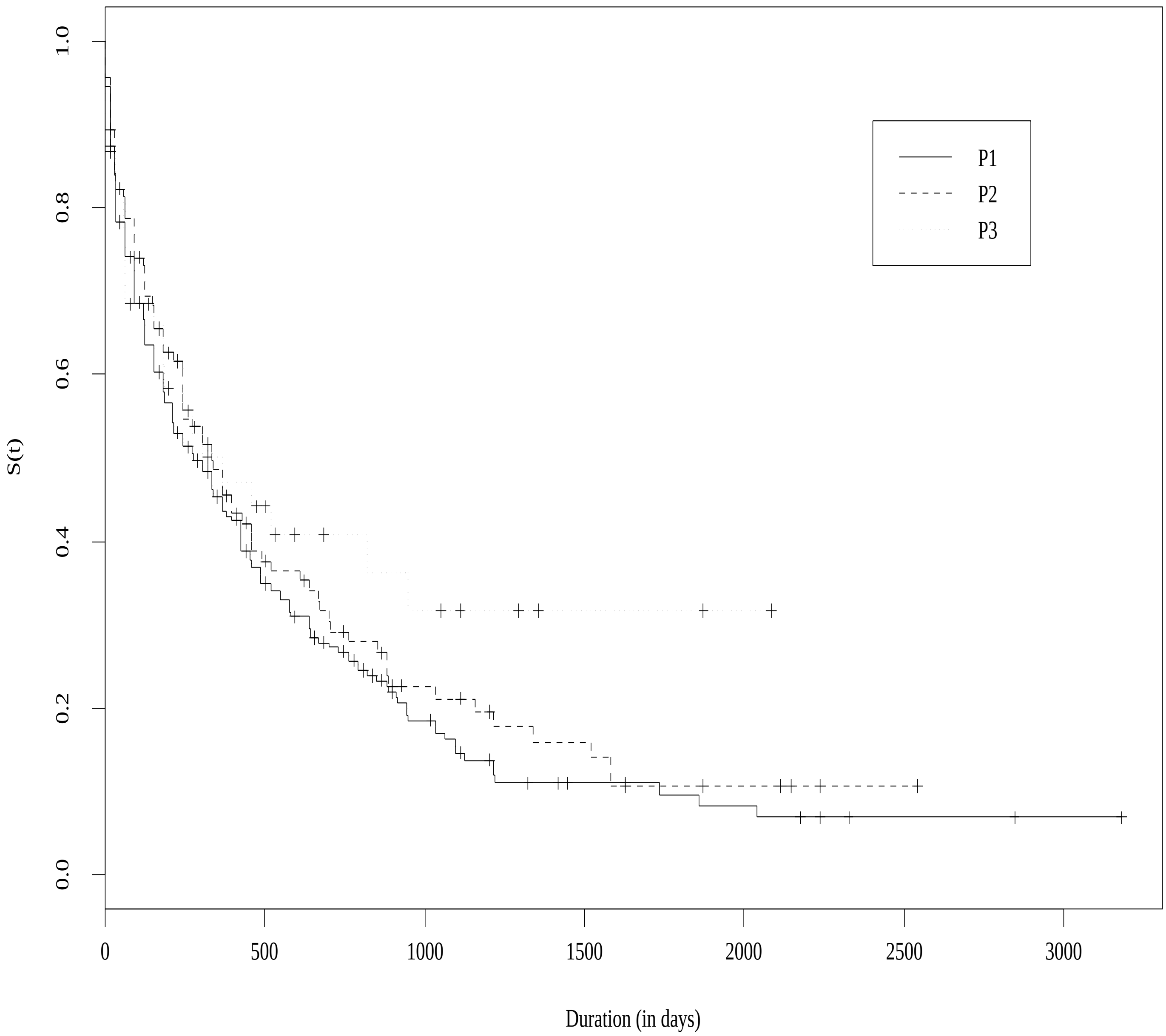

Figure 1: Kaplan-Meier curves for time on programs. The number of individuals in programs P1, P2 and P3 are 269, 113 and 45 respectively.

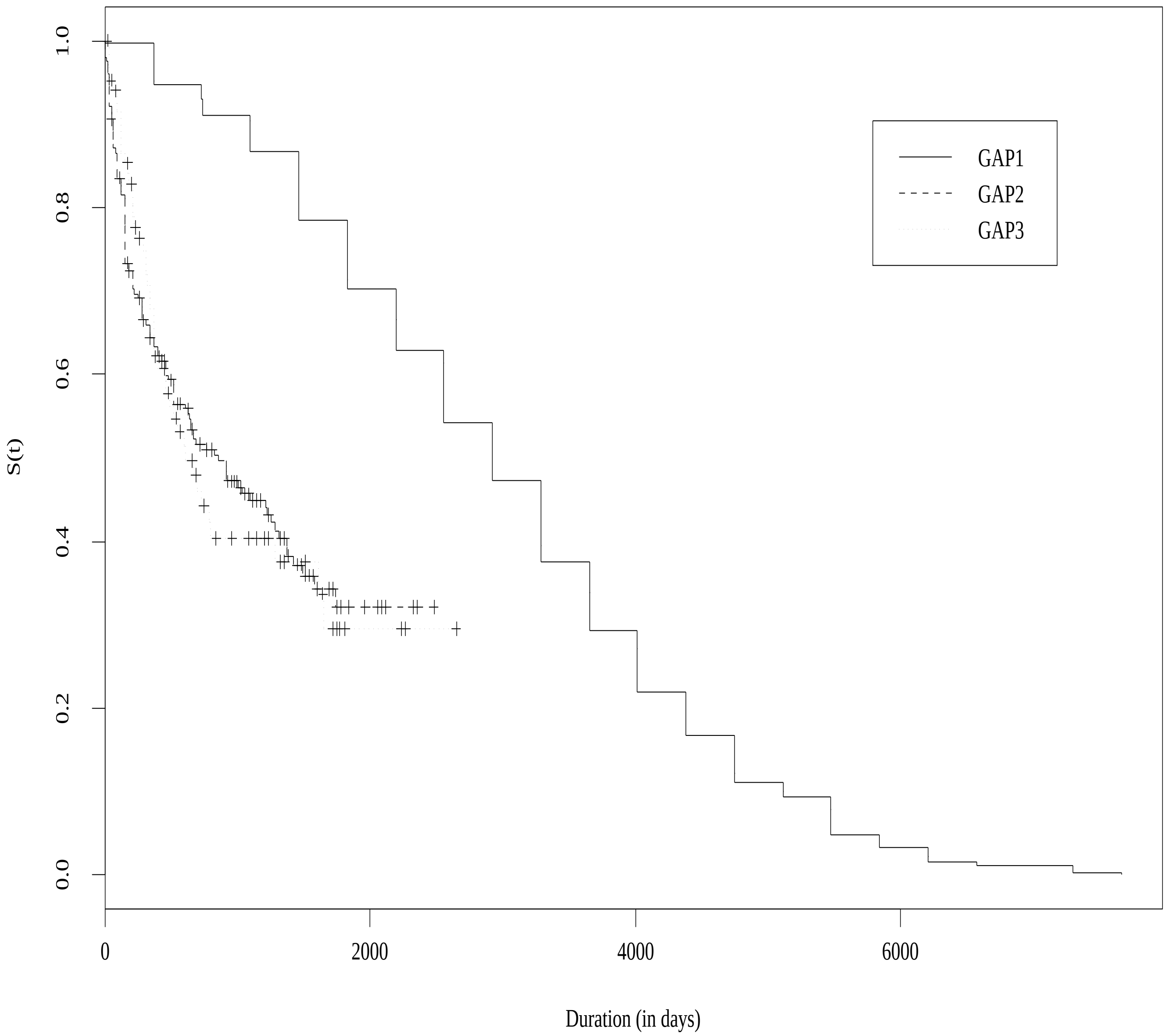

Figure 2: Kaplan-Meier curves for gap times.

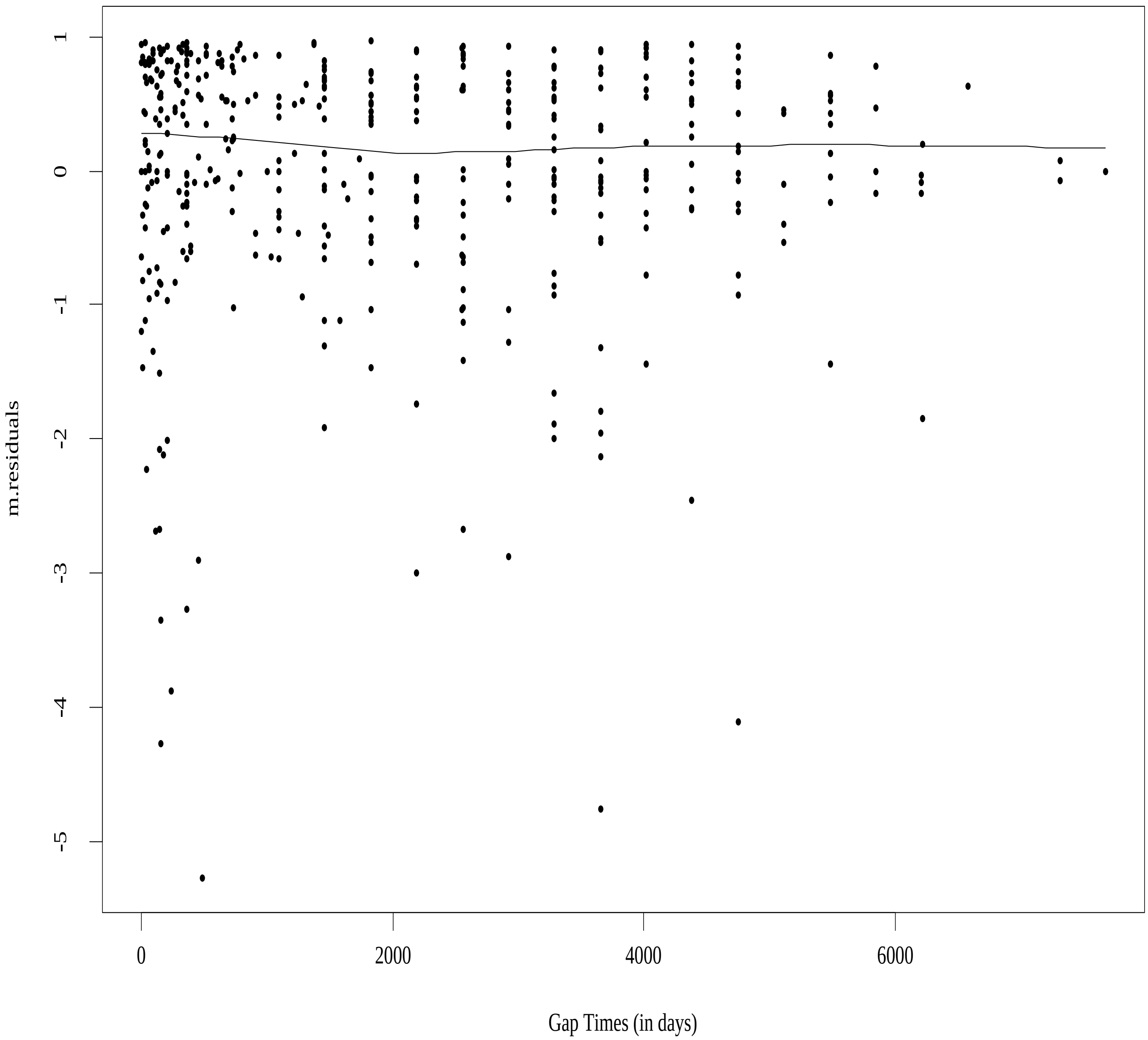

Figure 3: Martingale residual plots for model A, with loess scatterplot smoothing.

	Prevalent			Incident		
Covariate	$\hat{\boldsymbol{\beta}}$ (s.e.)	exp($\hat{\boldsymbol{\beta}}$)	P-value	$\hat{\boldsymbol{\beta}}$ (s.e.)	exp($\hat{\boldsymbol{\beta}}$)	P-value
HIV	-1.012 (0.256)	0.363	< 0.001	-0.945 (0.271)	0.389	< 0.001
HEPC	-1.744 (0.513)	0.175	< 0.001	-1.925 (0.524)	0.146	< 0.001
PRISON	0.291 (0.116)	1.338	0.012	*	*	*
TRANSFER	0.380 (0.095)	1.463	< 0.001	0.496 (0.106)	1.643	< 0.001
METHCHEM	-1.376 (0.174)	0.252	< 0.001	-1.395 (0.168)	0.248	< 0.001
URATEOP	0.373 (0.065)	1.453	< 0.001	0.388 (0.073)	1.474	< 0.001

Table 1: Results for best-fitting prevalent and incident Cox models for methadone program one (P1).

s.e. = standard error of $\hat{\boldsymbol{\beta}}$, * covariate not significant

	Prevalent			Incident		
Covariate	$\hat{\boldsymbol{\beta}}$ (s.e.)	exp($\hat{\boldsymbol{\beta}}$)	P-value	$\hat{\boldsymbol{\beta}}$ (s.e.)	exp($\hat{\boldsymbol{\beta}}$)	P-value
1STDOSE	-0.030 (0.009)	0.971	0.002	-0.023 (0.010)	0.977	0.024
METHCHEM	-0.880 (0.231)	0.414	< 0.001	-0.881 (0.250)	0.414	< 0.001
URATEOP	*	*	*	0.573 (0.153)	1.774	< 0.001

Table 2: Results for best-fitting prevalent and incident Cox models for methadone program two (P2).

	Prevalent			Incident		
Covariate	$\hat{\boldsymbol{\beta}}$ (s.e.)	exp($\hat{\boldsymbol{\beta}}$)	P-value	$\hat{\boldsymbol{\beta}}$ (s.e.)	exp($\hat{\boldsymbol{\beta}}$)	P-value
TRANSFER	1.244 (0.318)	3.468	< 0.001	*	*	*
METHCHEM	-1.190 (0.485)	0.304	0.014	-1.198 (0.526)	0.302	0.023
URATEOP	0.743 (0.198)	2.102	< 0.001	*	*	*
HEPC	*	*	*	-5.916 (0.002)	0.003	< 0.001
GAP1	*	*	*	0.001 (< 0.001)	1.001	0.017

Table 3: Results for best-fitting prevalent and incident Cox models for methadone program three (P3).

Covariate	$\hat{\boldsymbol{\beta}}$	'naive' s.e.	robust s.e.	$\exp(\hat{\boldsymbol{\beta}})$	P-value
PENTRY.85-88	-0.068	0.078	0.088	0.934	0.440
PENTRY.89-91	-0.129	0.055	0.061	0.879	0.036
HIV	-0.382	0.197	0.250	0.682	0.130
HEPC	-1.389	0.370	0.423	0.249	0.001
PRISON	0.378	0.197	0.178	1.460	0.034
TRANSFER	1.010	0.166	0.235	2.744	< 0.001
1STDOSE	-0.012	0.005	0.005	0.989	0.031
METHCHEM	-0.858	0.127	0.146	0.424	< 0.001
URATEOP	0.502	0.058	0.073	1.652	< 0.001
GAPS	0.0001	0.00004	0.00004	1.000	0.007

Table 4: Maximized partial likelihood estimates for truncation model A.

Covariate	$\hat{\boldsymbol{\beta}}$	'naive' s.e.	robust s.e.	$\exp(\hat{\boldsymbol{\beta}})$	P-value
PENTRY.85-88	-0.084	0.078	0.080	0.919	0.290
PENTRY.89-91	-0.154	0.055	0.057	0.857	0.006
HIV	-0.448	0.192	0.220	0.639	0.042
HEPC	-1.331	0.372	0.426	0.264	0.002
PRISON	0.417	0.193	0.169	1.518	0.013
TRANSFER	1.034	0.166	0.199	2.812	< 0.001
1STDOSE	0.010	0.005	0.005	0.990	0.037
METHCHEM	-0.720	0.129	0.123	0.487	< 0.001
URATEOP	0.478	0.059	0.061	1.612	< 0.001
GAPS	0.001	0.0002	0.0002	1.001	< 0.001

Table 5: Maximized partial likelihood estimates for model B.

Covariate	$\hat{\boldsymbol{\beta}}$	Standard error $\hat{\boldsymbol{\beta}}$	$\exp(\hat{\boldsymbol{\beta}})$	P-value
GAP1	0.0001	0.0001	1.000	0.009
GAP2	0.0005	0.0002	1.001	0.029
GAP3	-0.0004	0.0006	1.000	0.520

Table 6: Covariate effects for program-specific GAPS within multivariate model A.