THE ROLE OF FRAILTY MODELS AND ACCELERATED FAILURE TIME MODELS IN DESCRIBING HETEROGENEITY DUE TO OMITTED COVARIATES

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SUMMARY

In survival analysis, deviations from proportional hazards may sometimes by explained by unaccounted random heterogeneity, or frailty. This note recalls the literature on omitted covariates in survival analysis and shows in a case study how unstably frailty models might behave when asked to account for unobserved heterogeneity in standard survival analysis with no replications per heterogeneity unit. Accelerated failure time modelling seems to avoid these difficulties and also to yield easily interpretable results.

We propose that it would be advantageous to upgrade the accelerated failure time approach alongside the hazard modelling approach to survival analysis.

1. INTRODUCTION

Statistical modelling of heterogeneity may be based on stratification according to factors, regression on covariates, or by assuming a probability distribution of the interindividual variation. In survival analysis Vaupel et al.[1] coined the phrase "frailty" in connection with a particular version of such a stochastic model, in which individual i was assumed to have death intensity $Z_i\lambda(a)$ at age a, where the random variable Z_i (the "frailty") is assumed to have a gamma distribution. The assumptions that the randomness is age-independent and that it acts multiplicatively on an underlying intensity $\lambda(a)$ are in principle arbitrary but have been taken as the basis for much subsequent work on random heterogeneity in survival analysis. Useful surveys are by Andersen et al.[2], Chapter IX, Nielsen et al.[3], Klein et al.[4], Aalen[5], Schumacher et al.[6] and Hougaard[7]. The frailty models are likely to be particularly useful for modelling multivariate survival times, whether "serial" or "parallel", see a very interesting series of papers by Oakes[8], Pons et al.[9] and Prentice & Cai[10] with discussion by Turnbull[11]. The double role of the frailty distribution with finite mean in describing both nonproportionality and intraclass correlation was pointed out by Hougaard in several papers, e.g. Hougaard[12], and critically discussed by Yashin et al.[13] who suggested generalizations to separately account for overdispersion and correlation.

Robins and Greenland[14,15] questioned the general applicability of the hazard ratio as mediator of covariate effects, and Hougaard et al.'s[16] case study indicated approximate unidentifiabilities that seemed rather more satisfactorily solved by abandoning the hazard ratio in favour of the accelerated failure

time framework for interpretation of covariate effects in survival analysis with random heterogeneity.

The purpose of this note is to briefly recapitulate the above framework and to present another case study which, like that of Hougaard et al.[16], indicates that accelerated failure models may be preferable in accounting for (residual) heterogeneity in univariate ("single-spell") survival times due to "missing" (omitted, unrecorded) covariates.

Section 2 presents a brief partial survey on approaches to the study of omitted covariates in the 1980s, and Section 3 briefly recalls the proportional hazards frailty model with aspects of current techniques for its statistical analysis. Section 4 presents and slightly extends the Struthers-Kalbfleisch heuristics on omitted covariates in survival analysis based on a normal-theory linear model equivalent to the accelerated failure time model. Section 5 presents the example and Section 6 a concluding discussion.

2. EARLIER APPROACHES TO THE EFFECT OF OMITTING COVARIATES IN SURVIVAL ANALYSIS

A series of studies in the 1980s were concerned with the possible bias in the estimated treatment effect when important covariates were omitted. Gail et al.[17] and Chastang et al.[18] showed that for nonlinear models bias may result even when covariates are balanced, as would be the case when studying the treatment effect in a randomised experiment without accounting in the analysis for important covariates. However, this bias would be negligible for exponentially distributed survival data with moderate censoring.

Solomon[19] showed that regression parameters for the (Cox) proportional hazards model and the accelerated failure time model are often approximately proportional, so that qualitative inferences should be robust to model specification. Struthers & Kalbfleisch[20] showed that if one of two independent covariates is omitted then the effect of the other is underestimated. They used a heuristic analogue between an accelerated failure time model and normal-theory linear models which we elaborate in Section 4. Schumacher et al.[6] showed that ignoring a prognostic factor damps the estimated hazard ratio. Bretagnolle & Huber[21,22] gave a definitive exposition of this type of study, treating also the case of several covariates, in general confirming the above results on attenuation of effects if other important covariates are omitted. Gail[23] and (recently) Antes and Schmoor[24] gave surveys contrasting classical linear regression results with those of survival analysis.

Concluding the 1980s-literature in the area, Pepe et al.[25] gave a broad authoritative discussion cautioning against the practical utility of technical deattenuation procedures, these often being rather model-dependent.

3. THE PROPORTIONAL HAZARDS FRAILTY MODEL

The proportional hazards frailty model assumes that for given frailty variable Z_i and covariates X_i, individual i has hazard

$$\lambda_i(t) = Z_i \alpha(t) e^{\beta' X_i}$$

at time t. The model is then completed by assuming a parametric distribution for Z_i. If the dependence of $\alpha(t)$ on t is specified by finitely many

parameters, maximum likelihood estimation is in principle a routine matter. However based on the prominent place in survival analysis of the semiparametric proportional hazards model of Cox[26], interest has also focused on how to make statistical inference in the above frailty model, if $\alpha(t)$ is allowed to vary freely.

An EM algorithm approach is then possible, cf. Nielsen et al.[3], Klein[27] and Andersen et al.[2], Chapter IX, for details. The EM algorithm does not directly yield approximate standard errors of all estimates, and additional care is required (Andersen et al.[28]). These references did not contain mathematical proofs of asymptotic properties of the estimators and test statistics, but such results are being derived by Murphy[29,30].

4. STRUTHERS-KALBFLEISCH HEURISTICS

Struthers[31] and Struthers and Kalbfleisch[20] drew the following instructive parallel between the omitted variable problem in survival regression models and the conventional wisdom from normal-theory regression.

Assume two independent covariates x_1 and x_2 and the proportional hazards model

$$\lambda(t) = \lambda_0(t)e^{x_1\beta_1+x_2\beta_2}$$

in the particular case of Weibull underlying intensity

$$\lambda(t) = \kappa\nu t^{\nu-1}e^{x_1\beta_1+x_2\beta_2}.$$

Let W have a standard extreme value distribution of a minimum, that is, the density of W is $\exp(w - e^w), -\infty < w < \infty$. Then T
follows the above Weibull distribution, where

$$Y = \log T = -\frac{\log \kappa}{\nu} - \frac{\beta_1}{\nu} x_1 - \frac{\beta_2}{\nu} x_2 + \frac{W}{\nu}.$$

This is an *accelerated failure time model*: an ordinary regression problem of log(survival time) on x_1 and x_2 with extreme value distributed residuals with scale parameter ν^{-1}, regression coefficients $-\beta_1/\nu$ and $-\beta_2/\nu$ and intercept $-\nu^{-1} \log \kappa$. Borrowing experience from normal-theory linear regression (i.e. assuming W standard normal (0,1)), it is seen that the regression coefficients and intercept are estimated by the usual regression estimates, in particular $E(\widehat{\beta_1/\nu}) = \beta_1/\nu$, ν^{-1} is estimated by the usual residual empirical variance s^2, and for large samples, $\hat{\beta}_1 \xrightarrow{P} \beta_1$, and the asymptotic variance of $\hat{\beta}_1$ is

$$\frac{1}{n}\left(\frac{1}{\sigma_{x_1}^2} + \frac{\beta_1^2}{2}\right) \quad .$$

Assume now that rather than the regression of Y on (x_1, x_2), the regression of Y on x_1 only is considered. This may be written

$$Y = \gamma - \beta\tau x_1 + \tau W$$

with W again standard normal $(0, 1)$ but now, since $\tau^2 = \mathrm{Var}(Y \mid x_1)$, $\nu^{-1} = \mathrm{Var}(Y \mid x_1, x_2)$,

$$\tau^2 = \nu^{-1}(1 + \beta_2^2 \sigma_{x_2}^2)\nu^{-1} \quad .$$

As above, $\beta\tau$ is estimated by the usual regression estimate, so $E(\widehat{\beta\tau}) = \beta\tau = \beta_1/\nu$ (= the theoretical regression of Y on x_1). Therefore $\hat{\beta} \xrightarrow{P} \beta = \beta_1\nu^{-1/2}/\tau$, which is closer to 0 than β_1: there is the well-known *attenuation due to an omitted covariate*. Furthermore

$$\text{as. var.}(\hat{\beta}) = \frac{1}{n}\left(\frac{1}{\sigma_{x_1}^2} + \frac{\beta_1^2}{2\nu\tau^2}\right) < \text{as. var.}(\hat{\beta}_1) \quad ;$$

the standard error is also attenuated, indeed if $\sigma_{x_1}^2$ is large, the Wald-t-statistics are similar:

$$\hat{\beta}_1/\widehat{s.d.}(\hat{\beta}_1) \approx \hat{\beta}/\widehat{s.d.}(\hat{\beta}).$$

Weibull frailty model.

Assume now that x_2 is not observed but that instead a frailty random variable Z is multiplied onto the proportional hazards model, to yield

$$\lambda(t|Z) = Z\kappa\nu t^{\nu-1}e^{x_1\beta_1} \quad .$$

This corresponds to

$$Y = \log T = -\frac{\log\kappa}{\nu} - \frac{\beta_1}{\nu}x_1 + \frac{W}{\nu} + \frac{U}{\nu} \quad ,$$

where $U = -\log Z$ independent of the extreme value distributed W.

This is again an accelerated failure time model with intercept $-\nu^{-1}\log\kappa$ and regression coefficient $-\beta_1/\nu$ (same as before), only the residual distri-

bution has changed, now being that of $(W+U)/\nu$. Again borrowing experience from normal-theory linear regression, $-\beta_1/\nu$ would be estimated by the usual regression estimate, $E(\widehat{\beta_1/\nu}) = \beta_1/\nu$, but if we had erroneously assumed no frailty ($U=0$), $\nu-1$ would have been overestimated by the factor $\eta = (\mathrm{Var}W + \mathrm{Var}U)/\mathrm{Var}W$ and the hazard model regression parameter $\beta_1 = (\beta_1/\nu)/\nu^{-1}$ similarly underestimated by the factor $\eta 1$, leading to *attenuation by disregarding frailty.*

Conclusion. For the Weibull model the accelerated failure time parametrization conveniently separates regression coefficients from dispersion parameters, allowing unchanged estimation of regression coefficients under the frailty-amended model, which only contributes to the dispersion. This was previously pointed out by Hougaard et al.[16].

5. EXAMPLE

Andersen et al.[2] considered in their Examples VII.3.1, VII.3.4 and IX.4.3 survival after operation for malignant melanoma for 205 patients from Odense, Denmark. Of these, 57 died from the disease in the follow-up period, while the 14 who died from other causes and the remaining 134 who were alive at the end of follow-up were considered censorings. A number of clinical and histological covariates were registered at entry. Andersen et al. fitted a Cox regression model and after careful analysis concluded that only the binary covariate ulceration and the continuous covariate log(tumour thickness) were required to obtain an adequate description. There were several somewhat

similar ways of incorporating these covariates. If the covariates are included in a standard Cox model the estimated regression coefficients and standard errors were

log(tumour thickness)	0.610 (0.176)
ulceration	0.971 (0.321)

but graphical checks (Andersen et al.[2], Figs. VII.3.3 and VII.3.6) raised some suspicion that hazards for patients without and with ulceration, were not proportional but rather converging. Therefore a time-dependent covariate to account for possible time $\times$ covariate interaction was added:

log(tumour thickness)	0.607 (0.177)
ulceration	1.082 (0.357)
ulceration $\cdot(\log(t) - 7)$	-1.198 (0.589);

here t is measured in days and $7 \sim \log(3 \times 365)$. A likelihood ratio test of no effect of the latter variable yielded $P = .02$, giving some evidence to support the suspected deviation from proportionality.

Semiparametric frailty model.

Because this deviation might be interpreted as a selection effect in a heterogeneous population arising from important unmeasured confounders not being included in the analysis, a frailty model was postulated. To the

Cox regression model specification of the death intensity with the two covariates was multiplied a frailty factor Z, assumed gamma distributed with $E(Z) = 1, \mathrm{Var}(Z) = \delta$. The fitted parameters were (with the no-frailty model estimates attached for comparison)

	Frailty	No frailty
log(tumour thickness)	1.370 (0.472)	0.610 (0.176)
ulceration	1.696 (0.686)	0.971 (0.321)
frailty variance	4.215 (2.266)	0 (-)

with likelihood ratio test statistic of no frailty variance yielding $P = .007$. For details on estimating the standard errors under the frailty model, cf. Andersen et al.[27].

It is thus seen that incorporation of unmeasured population heterogeneity in this case *deattenuates* the effects of the measured covariates (as well as of their standard errors) by a factor of about 2.

Weibull frailty model.

Andersen et al.[2] noted that the underlying intensities of the fitted Cox regression models varied so regularly that a hypothesis of Weibull underlying intensity should be acceptable. In order to study the role of the choice of frailty distribution on the above effects, we therefore also considered proportional hazards models with Weibull underlying intensity and three frailty distributions: gamma, positive stable, and inverse Gaussian, cf. the sur-

vey by Klein et al.[4], as well as the power variance family $P(\alpha, \psi, \xi)$ due to Hougaard[32], of which all of these are special cases. Hougaard's model is most easily characterized by the Laplace transform

$$\exp\left\{-\frac{\psi}{\alpha}\left[(\xi+s)^{\alpha}-\xi^{\alpha}\right]\right\} \quad .$$

Our gamma distribution is $P(0, \delta^{-1}, \delta^{-1})$, while $P(\alpha, \psi, 0)(0 < \alpha < 1)$ are the positive stable distributions and $P(\frac{1}{2}, \psi, \xi)$ the inverse Gaussian distributions. As is well known, the positive stable frailty distribution leads to unidentifiability in the present case of observing only one event per individual. For the other frailty models, with the no frailty model included for comparison, the estimates are given in Table 1.

It is seen that the results from the all-inclusive power variance frailty model are virtually indistinguishable from that of the gamma frailty model, which in turn fits significantly better than the inverse Gaussian frailty and the no frailty/positive stable frailty (the latter two having the same likelihood). Also, the estimates for no frailty and gamma frailty are well compatible with the semiparametric estimates quoted above, and also there is a deattenuation factor of 2 to 3 on the regression parameter when considering the gamma frailty model. The assumption of inverse Gaussian frailty yields intermediate results, and judging from the likelihood also a less effective accounting for the heterogeneity.

Table 2 records the estimated correlations between the estimated frailty parameter (indicating the spread of the frailty distribution) and the estimates of the regression coefficients and the Weibull shape parameter. The positive

correlation reflects the inherent negative correlation between two alternative ways of describing the observed heterogeneity in survival times: either by a large frailty parameter (wide frailty distribution), or by a "flat" underlying intensity (small Weibull shape parameter). Indeed, while the underlying Weibull distribution in the no-frailty model is insignificantly different from an exponential distribution (shape parameter=1), a much more concentrated underlying distribution is estimated for the gamma and inverse Gaussian frailty models.

The positive correlations between estimated frailty parameter and estimated regression parameters reflect the deattenuation effect described in Section 3. Intuitively: The interindividual variation is *either* described by covariates (high regression coefficients) *or* frailty (large frailty parameter).

Accelerated failure time interpretation.

Alternatively, we may start from the accelerated failure time (AFT) interpretation outlined towards the end of Section 3. We then obtain the results of Table 3, accounting for the multiplicative indeterminacy in the positive stable frailty distribution and still assuming underlying Weibull distribution.

It is seen that in the AFT interpretation, the various models agree. Let us emphasize that the AFT interpretation is actually very intuitive: we have estimated that (taking the best fitting gamma frailty model as example)

$$\begin{aligned} \log(\text{survival time}) = \text{const.} \quad &- \quad 0.60 \times \log \text{ tumour thickness} \\ &- \quad 0.75 \times \text{ulceration} \\ &+ \quad \text{noise} \quad . \end{aligned}$$

That is, for fixed value of ulceration, if tumour thickness increases by a factor α, survival time will decrease by a factor $\alpha^{0.60}$. Similarly, for fixed value of tumour thickness, ulceration of the tumour will decrease life by a factor of $e^{-0.75} \approx 0.47$ compared to what it would have been if the tumour was not ulcerated.

6. DISCUSSION

Frailty interpretation: individual or population risk. The original impetus for the frailty concept such as defined by Vaupel et al.[1] was to clarify the behaviour of the *mean hazard among the survivors* in a heterogeneous population. In our example we observed a (slight) deviation from proportional hazards when assuming no heterogeneity beyond that given by the covariates tumour thickness and ulceration. The convergence of the "population" risk of the survivors could be explained by a statistically significant unobserved heterogeneity in a model with proportional individual hazards. These results were maintained whether the underlying intensity was allowed to vary freely or restricted to having a Weibull parametric form, and the best fit among the tested frailty models was obtained by the gamma frailty distribution, for which the deattenuation effect was estimated as about 2 to 3. However for

the only slightly worse fitting inverse Gaussian frailty distribution deattenuation was halved, and for the positive stable frailty model it (the parameter θ above) is inherently unidentifiable. (Motivated in part by this feature of the positive stable frailty distribution, Robins and Greenland[14,15] discussed consequences of such unidentifiability problems for compensation schemes). It is well known that ratios of regression coefficients are much less sensitive to model misspecification than the regression coefficients themselves, see Solomon[19] for examples from the present context and Li and Duan[31] for a careful general discussion with review of earlier work. This is also very apparent in our example.

A conceptual explanation may be obtained from the observation above about strong positive correlation between the estimates of the Weibull shape parameter ν and the spread of the frailty distribution. The single-spell data contain only limited power as to distinguishing the random variation as within-individual (large ν) or between-individual (large frailty spread), and therefore interpretations based only on the within-individual hazard are unstable.

Accelerated failure time interpretation: As seen above the AFT interpretation (which was here feasible starting from log-Weibull error distribution) avoids the unidentifiability problem by shifting attention of the dependence on covariates from the elusive concept of 'individual hazard' to the acceleration factor of the life time itself, thereby combining the within- and between-individual components of variation into much more stably determined functionals. The heterogeneity is conveniently relegated to an overdispersion

element, and the interpretation is easy, direct and uncontroversial. Notice that the well-determined ratio of the hazard rate regression coefficients is also the ratio of the AFT regression coefficients.

A referee has remarked that the linearity of the AFT is what yields the independence of regression estimates and frailty distribution, and that a similar effect could be obtained by formulating a linear model for the hazard. Such a model has been extensively discussed by Aalen[34].

Conclusion. Stable estimation of hazard rate regression coefficients in the frailty models requires precise knowledge of the frailty distribution, and this will often be hard to expect from single-spell data. In this case the accelerated failure time parametrization offers an attractive alternative.

Acknowledgements. An early and incomplete presentation of the above case study at the workshop in Freiburg in February, 1995, generated a series of very useful comments and criticisms, and later discussions with other colleagues have also been helpful. The present version therefore owes much to comments from Norman E. Breslow, Mitchell Gail, James M. Robins, Richard D. Gill, Peter Sasieni, Gerhard Arminger, Jrgen Hilden, Philip Hougaard and two referees. Per Kragh Andersen is half-time employed at the Danish Epidemiology Science Center whose activities are supported by a grant from the Danish National Research Foundation. This research was supported by contract 2R01 CA54706-04A1 from the National Cancer Institute.

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Table 1. Estimates for Weibull frailty models.

Frailty distribution	Power variance	Gamma	Inverse Gaussian	No
Weibull shape parameter	2.83 (.817)	2.917 (0.718)	1.747 (0.299)	1.150 (0.131)
log(tumour thickness)	1.717 (.607)	1.754 (0.592)	0.932 (0.281)	0.577 (0.175)
ulceration	2.069 (.995)	2.180 (0.875)	1.512 (0.518)	1.020 (0.322)
-2 log likelihood	1074.84	1074.88	1083.14	1093.90
Likelihood ratio				
test for no frailty, P	¡.0001	¡.0001	.003	

Table 2. Weibull frailty models. Correlations between estimated frailty parameter and parameter estimates as specified.

	Gamma frailty semiparametric	Gamma frailty Weibull	Inverse Gaussian frailty Weibull
Weibull shape parameter	—	.882	.793
log(tumour thickness)	.632	.598	.323
ulceration	.532	.511	.430

Table 3. Weibull frailty models. Hazard rate regression coefficients contrasted to accelerated failure time regression coefficients.

	Gamma frailty	Inverse Gaussian frailty	No frailty (θ assumed=1) or Positive stable frailty (θ indeterminate)
Weibull shape parameter	2.917 (0.718)	1.747 (0.299)	$1.150 \cdot \theta$ $(0.131 \cdot \theta)$
log(tumour thickness)	1.754 (0.592)	0.932 (0.281)	$0.577 \cdot \theta$ $(0.175 \cdot \theta)$
ulceration	2.180 (0.875)	1.512 (0.518)	$1.020 \cdot \theta$ $(0.322 \cdot \theta)$
$\frac{\text{log(tumour thickness)}}{\text{Weibull shape parameter}}$	0.60 (0.15)	0.53 (0.18)	0.50 (0.16)
$\frac{\text{ulceration}}{\text{Weibull shape parameter}}$	0.75 (0.25)	0.87 (0.28)	0.89 (0.29)