行政院國家科學委員會專題研究計畫　成果報告

涵蓋結構下相對涉險迴歸模式之估計效率、訊息界限與適合度研究

計畫類別：個別型計畫
計畫編號：NSC94-2118-M-039-001-
執行期間：94 年 08 月 01 日至 95 年 07 月 31 日
執行單位：中國醫藥大學公共衛生學系

計畫主持人：吳宏達

報告類型：精簡報告

處理方式：本計畫可公開查詢

中　華　民　國 95 年 10 月 30 日

A Varying-Coefficient Hazards Regression Model for Multiple Cross-Effect

Hong-Dar Isaac Wu,
School of Public Health and Biostatistics Center, China Medical University,
91 Hsueh-Shih Rd., Taichung 404, Taiwan.
E-mail: honda@mail.cmu.edu.tw

2006 October 27

Abstract

We consider a piecewise-constant varying-coefficient model to account for survival data with multiple crossings. Estimating procedures are provided, and a class of tests is constructed for the need of imposing varying coefficients for some specific covariates, or for some other purposes. Analysis of the survival of Taiwan's stroke patients is reported to illustrate the applications.

Key Words: time-varying effect, heteroscedasticity, multiple crossings, proportional hazards, non-proportional hazards.

1 Introduction

In event-history data analysis where the effect of a specific variable is of the main interest, the problem of dealing with time-varying effect gets more important in the recent years. In contrast with the proportional hazards (PH) model (Cox, 1972), many authors have devoted to the study of varying-coefficient PH (PH^{VC}) model. For example, see Murphy and Sen (1991), Murphy (1993), Martinussen and Scheike (2006), and Tien, Zucker, and Wei (2005) among others. Without regard to the space of 'time', the PH^{VC} model basically still estimate homogeneity effect over the space of covariate(s). By this, *homogeneity* means there is a common 'effect' between two covariate-specific subpopulations represented by different values of the covariate, say Z, or of the 'configurations' of several covariates. On the contrary, *heterogeneity* states that the effect is different and diverse over the covariate space of Z. The variable Z can either be observed or unobserved. Examples of modeling observed and unobserved heterogenity include the heteroscedastic hazards regression (HHR) model (Hsieh, 2001) and the frailty model (Vaupel, 1979; Hougaard, 1986), respectively. This study focuses on the former case. In addition to capturing heterogeneity effect, the HHR model also has the merit of modeling time-varying effect by the hazard function:

$$\lambda(t;\mathbf{z},\mathbf{x}) = \lambda_0(t)e^{\gamma^T\mathbf{x}(t)}\{\Lambda_0(t)\}^{e^{\gamma^T\mathbf{x}(t)}-1}e^{\beta^T\mathbf{z}(t)}, \tag{1}$$

where $\mathbf{z}(t)$ and $\mathbf{x}(t)$ are two sets of predictable time-dependent covariates, and $\Lambda_0(t) = \int_0^t \lambda_0(u)du$ is the baseline cumulative hazard. In view of the intrinsic time-varying property of the hazard ratio implied by (1), it is possible to extend the HHR model to incorporate varying-coefficient settings. Hereafter we denote the varying-coefficient HHR model as an HHR^{VC} model with its functional form stated in Section 2. Contrasting with the PH model, the most significant parts are certainly to make feasible the incorporation of parameter γ, and to convince the use of time-varying $\beta(t)$ and $\gamma(t)$ (see (2) below). Motivation of this extension can be interpreted

as follows. First, the inter-relation among groups in terms of survivor or cumulative hazard functions may be 'diverse' in time. An apparent phenomenon is the multiple cross-effect (MCE) studied by Bagdonavičius and Nikulin (2006). Second, cure-fraction (CF) appeared in many clinical and oncological studies in which the survival of cancer patients receiving surgery followed by (or prior to) chemo- and/or radio-therapies are of concern. Though, the definition of 'cure' still needs to be clarified. The probability of cure needs to be handled. Finally, if the data cannot be suitably described by a simpler model (such as the PH or PH^{VC} model) and can be well described by the extended model (such as the HHR^{VC}), it is also sensible to consider the extended class from the viewpoint of model fitting.

The HHR^{VC} model can deal with survival data with time-diversity (e.g., MCE) and cure-fraction simultaneously, within a reasonable range of observational period. The purpose of this paper is to study relevant applications of the HHR^{VC} model in the aspects of data practition and model validity. For the latter, we assume HHR^{VC} as the alternative hypothesis and test whether the varying-coefficient setting can be further simplified. Section 2 of this article introduces the piecewise-constant setting of the HHR^{VC} model. Estimation and model validity procedures are provided in Sections 3 and 4. We report in Section 5 actual data analysis concerning the mortality of stroke patients with comorbidities. Finally, implications of the varying-coefficient model and some practical issues of data analysis are discussed.

2 Illustration of The Piecewise Constant Model

Piecewise-constant setting

Model (1) can be extended to allow for varying coefficients:

$$\lambda_{\mathbf{z},\mathbf{x}}(t) = \lambda_0(t)\{\Lambda_0(t)\}^{e^{\gamma(t)\mathbf{z}}-1} e^{\beta(t)\mathbf{z}+\gamma(t)\mathbf{x}}. \tag{2}$$

where $e^{\beta(t)\mathbf{z}}$ is referred to as the *risk function*, and $e^{\gamma(t)\mathbf{x}}$ as the *heteroscedasticity component*. For an easy exposition, we adopt notations only with 'univariate' case and, in the sequel, $\mathbf{z} = \mathbf{x}$.

Because the partial likelihood does not eliminate out the baseline hazard, there are three time-dependent parameters, ($\Lambda_0(t)$ (or $\lambda_0(t)$), $\beta(t)$ and $\gamma(t)$) to be estimated simulataneously. We use the *piecewise-constant approximation* method (Murphy and Sen, 1991; Murphy, 1993; Marzec and Marzec, 1997) to make it compatible with the approach of Hsieh (2001). Let $[0, \tau]$ be the observational period, and $0 = \tau_0 < \tau_1 < \ldots < \tau_m = \tau$ be a set of cutoff points. The following piecewise-constant approximations are adopted:

$$\begin{aligned} \overline{\Lambda}_0(t) &= \int_0^t \sum_1^m \alpha_j \mathbf{1}_{(\tau_{j-1}<u\leq\tau_j)} du, \\ \overline{\beta}(t) &= \sum_1^m \beta_j \mathbf{1}_{(\tau_{j-1}<t\leq\tau_j)}, \\ \overline{\gamma}(t) &= \sum_1^m \gamma_j \mathbf{1}_{(\tau_{j-1}<t\leq\tau_j)}. \end{aligned} \tag{3}$$

So the HHR^{VC} model considered in this paper has the following 'pieces' of hazard and cumulative hazard:

$$\begin{aligned} \overline{\lambda}(t;\mathbf{z}) &= \alpha_j \{\overline{\Lambda}_0(t)\}^{\sigma_j - 1} \sigma_j \mu_j, \tau_{j-1} < t \leq \tau_j, \\ \overline{\Lambda}(t;\mathbf{z}) &= \overline{\Lambda}(\tau_{j-1};\mathbf{z}) + [\{\overline{\Lambda}_0(t)\}^{\sigma_j} - \{\overline{\Lambda}_0(\tau_{j-1})\}^{\sigma_j}]\mu_j, \tau_{j-1} < t \leq \tau_j, \end{aligned} \tag{4}$$

where $\overline{\lambda}(\cdot)$ denotes the approximation of $\lambda(\cdot)$, $\sigma_j = e^{\gamma_j^T \mathbf{z}}$, $\mu_j = e^{\beta_j^T \mathbf{z}}$, and $\overline{\Lambda}(\tau_0;\mathbf{z}) = \overline{\Lambda}_0(\tau_0) = 0$. Formula (4) is very useful to understand the HHR^{VC} model and the accompanying random number generation in simulation studies. (Because we can simply use the relation $S(\cdot) = \exp\{-\Lambda(\cdot)\}$, and equate it to a Uniform(0,1)-random number.)

The reasons why we consider (2) (or (4)) for modeling multiple-crossings are: (i) The HHR model without varying coefficient gives only a *one-time crossing*. (ii) Although the PH model with varying-coefficient risk function produces multiple crossings, the inter-subpopulation effect is still homogeneous *at any fixed time point*. An example of data analysis in Section 5 illustrates the feasibitity; where the probability of 'cure' is actually a heterogeneity effect. By model (2), suitably modulating the baseline hazard also contributes to model 'multiple cross-effects plus

cure-fraction', albeit a *monotonic* $\gamma(t)$ is inevitably demanded.

3 Estimation under the Piecewise-constant Setting

Suppose there are n randomly right-censored observations $T_1 < T_2 < \ldots < T_n$, which can be survival or censoring times. Let $\lambda_i(t; \mathbf{z}(t), \mathbf{x}(t))$,$N_i(t)$ and $Y_i(t))$ be the intensity process, counting process and the associated at-risk indicator for the ith individual at time t, and denotes

$$S_{\mathbf{J}}(t) = (1/n) \sum_{i=1}^{n} Y_i(t) \mathbf{J}(t) \mathrm{e}^{\overline{\beta}(t)\mathbf{z}_i + \overline{\gamma}(t)\mathbf{x}_i} \{\overline{\Lambda}_0(t)\}^{\mathrm{e}^{\overline{\gamma}(t)\mathbf{x}_i - 1}}, \tag{5}$$

with possibly time-dependent covariates $\mathbf{J}(t) = 1, \mathbf{z}_i(t), \mathbf{x}_i(t)$, or $\mathbf{v}_i(t) \equiv \mathbf{x}_i(t)\{1 + \mathrm{e}^{\overline{\gamma}(t)\mathbf{x}_i} \log \overline{\Lambda}_0(t)\}$. It is straightforward to use the following Breslow-type equation (6) for the baseline cumulative hazard and estimating equations (7) and (8) for β_js and γ_js:

$$\overline{\Lambda}_0(t) = \sum_{i=1}^{n} \int_0^t \frac{dN_i(u)}{nS_1(u)}, \tag{6}$$

$$M_{2j} \equiv \quad \frac{1}{\sqrt{n_j}} \sum_{i=1}^{n} \int_{\tau_{j-1}}^{\tau_j} \{\mathbf{z}_i - \frac{S_{\mathbf{z}}}{S_1}\} dN_i(u) = 0, j = 1, 2, \ldots, m, \text{ and} \tag{7}$$

$$M_{3j} \equiv \quad \frac{1}{\sqrt{n_j}} \sum_{i=1}^{n} \int_{\tau_{j-1}}^{\tau_j} \{\mathbf{v}_i - \frac{S_{\mathbf{v}}}{S_1}\} dN_i(u) = 0, j = 1, 2, \ldots, m, \tag{8}$$

In addition, $\mathbf{M}_j = (M_{2j}, M_{3j})^T$, and A_j with elements

$$A_{j,ll'} = (1/n) \sum \int \mathrm{E}\{dM_{lj}(u) dM_{l'j}(u)\} du, \ (l, l' = 2, 3)$$

is the 'covariation' matrix between M_{2j} and M_{3j}. By imposing several technical conditions, large-sample properties of $\{(\widehat{\beta}_j, \widehat{\gamma}_j)\}_{j=1}^m$ and $\widehat{\Lambda}_0(t)$ can be established.

4 The Tests

In this section we study the HHR$^{\text{VC}}$ model, starting from the consideration of the following statistic (Hsieh, 2001; Wu et al., 2002):

$$\mathcal{T}_{\mathbf{degen}} = \sum_{j=1}^{m} \{\mathbf{M}_j^T \mathcal{A}_j^{-1} \mathbf{M}_j\}_{(\widehat{\beta}_j, \widehat{\gamma}_j, \widehat{\Lambda}_0)}$$

with the parameters of interest being evaluated piecewisely at $(\beta_j, \gamma_j) = (\widehat{\beta}_j, \widehat{\gamma}_j), \forall j$, where $\widehat{\beta}_j$ and $\widehat{\gamma}_j$ are the piecewise estimates solved from (7) and (8). The statistic $T_{\mathbf{degen}}$ has a degenerate value of 0; named as being *degenerate* because all degrees of freedom were *consumed out* at each segment. However it offers an important clue to constructing tests for model validity. For example, the test studied in Wu et al. (2002) can be viewed as a special case when the HHR model is treated as a submodel of HHR$^{\text{VC}}$. By this perspective, $\mathcal{T}_{\mathbf{degen}}$ can be amended to augment the degrees of freedom to $2m-2$ for the purpose of testing the validity of the HHR model, simply by repalceing all β_js and γ_js with the 'overall' estimates $\widehat{\beta}$ and $\widehat{\gamma}$ respectively, and by using $\mathcal{A}_j^{\circ}$ defined below instead of $\mathcal{A}_j$.

4.1 Some specific tests

The test considered in this section is constructed by assuming that the HHR$^{\text{VC}}$ model is true, and then test for a subset of the parameters at a given value. Now we define some notations used in the following context. For example, if $\theta = (\theta_1, \ldots, \theta_p)$ and $\theta_{\mathbf{k}} = (\theta_1, \theta_2)$ be a subset of θ, then $\theta_{(\mathbf{k})} \equiv \theta \backslash \theta_{\mathbf{k}} = (\theta_3, \theta_4, \ldots, \theta_p)$, and $\theta = \theta_{\mathbf{k}} \cup \theta_{(\mathbf{k})} = \theta_{(\mathbf{k})} \cup \theta_{\mathbf{k}}$. In this case, $\omega_{\mathbf{k}} = \{1, 2\}$, and $\omega_{(\mathbf{k})} = \{3, 4, \ldots, p\}$. Moreover $\widetilde{\mathbf{M}} = (M_{21}, \ldots, M_{2m}, M_{31}, \ldots, M_{3m})$, and, if $\theta_{\mathbf{k}^*} = (\theta_1, \theta_3)$, then $\theta_{\mathbf{k}} \backslash \theta_{\mathbf{k}^*} = \theta_2$ and $\theta_{\mathbf{k}} \cap \theta_{\mathbf{k}^*} = \theta_1$. We say in this example that $\theta_{\mathbf{k}}$ is the $\mathbf{k}$-component of θ. Hereafter let us define $\theta = (\beta_1, \ldots, \beta_m, \gamma_1, \ldots, \gamma_m)$. In order to test the hypothesis $H_0 : \theta_{\mathbf{k}} = \theta_{\mathbf{k}0}$, versus $H_a : \theta_{\mathbf{k}} \neq \theta_{\mathbf{k}0}$ at some $\theta_{\mathbf{k}0}$, the proposed statistic is:

$$\mathcal{T}_{\mathbf{k}} = \sum_{j=1}^{m} \{\widetilde{\mathbf{M}}_j^T \widetilde{\mathcal{A}}_j^{\circ -1} \widetilde{\mathbf{M}}_j\}_{\widehat{\theta}_{(\mathbf{k})} \cup \theta_{\mathbf{k}0}},$$

for which $\widetilde{\mathbf{M}}_j^T = (M_{2j}, M_{3j}) \cap \{M_l \in \widetilde{\mathbf{M}} : l \in \omega_{\mathbf{k}}\}$ and $\widetilde{\mathcal{A}}_j^{\circ^{-1}} = \{\widetilde{\mathbf{A}}_{j,kk} - \widetilde{\mathbf{A}}_{j,k(k)}\widetilde{\mathbf{A}}_{j,(k)(k)}^{-1}\widetilde{\mathbf{A}}_{j,(k)k}\}^{-1}$ with $\widetilde{\mathbf{A}}_j$ being the covariation submatrix of $\widetilde{\mathbf{M}}$ associated with the $\mathbf{k}$-component. Here a submatrix $\mathbf{B}_{k(k^*)}$ of $\mathbf{B}$ is defined as only keeping the $\mathbf{k}$-component of $\mathbf{B}$ *in row* and with 'deleting the $\mathbf{k}^*$-component of $\mathbf{B}$' *in column*, and so on. Note that $\mathcal{T}_{\mathbf{k}}$ is basically a score-type test. Another useful test to be compared with the above $\mathcal{T}_{\mathbf{k}}$-test is the (full-) likelihood ratio test, which is not discussed in the present study.

Test for varying effect of a specific covariate

If the HHR$^{\text{VC}}$ is the underlying model and piecewise-constant approximation is utilized, then the $T_{\{\cdot\}}$-statistic can be amended to test for 'varying effect' *with respect to a specific covariate*. For example, if we want to test for constant heteroscedasticity (that is, $\gamma(t) = \gamma_0, \forall t$, for some constant γ_0), the test statistic can be constructed as

$$\mathcal{T} = \sum_{j=1}^{m} \{\widetilde{\mathbf{M}}_j^T \widetilde{\mathcal{A}}_j^{\circ^{-1}} \widetilde{\mathbf{M}}_j\}_{(\widehat{\beta}_j, \gamma_0, \widehat{\Lambda}_0)}.$$

In practice γ_0 is substituted by an overall estimate $\widehat{\gamma}$. That is, assuming the HHR$^{\text{VC}}$ model, our hypotheses are $H_0 : \gamma_1 = \ldots = \gamma_m = \gamma_0$ versus $H_a : \gamma_j$'s are not all equal. If we set $\gamma_0 = \widehat{\gamma}$, the statistic $T_{\{\cdot\}}$ will be a χ^2_{m-1}-variate approximately.

Test for the varying-coefficient PH model

There are tests and diagnostic plots proposed to check for varying effects under the PH$^{\text{VC}}$-based framework (Murphy, 1993; Valsecchi et al., 1996; Marzec and Marzec, 1997; Martinussen and Scheike, 2006.) Here we propose a test $\mathcal{T}_{\mathbf{phvc}}$ for the PH$^{\text{VC}}$ model by assuming HHR$^{\text{VC}}$ as the alternative hypothesis. This $\mathcal{T}_{\mathbf{phvc}}$-test can be compared with the performance of several tests proposed in Marzec and Marzec (1997) (which are 'omnibus'). To this purpose, $\mathcal{T}_{\mathbf{phvc}}$ has the same form with $\mathcal{T}_{\mathbf{k}}$, except for being evaluated at $(\widehat{\beta_j}, 0, \widehat{\Lambda}_0)$ at the j-th segment. Under the hypotheses H_0: $\gamma_j = 0, \forall j$ versus H_a: at least one of the γ_js is not equal to 0, $\mathcal{T}_{\mathbf{phvc}}$ is distributed as χ^2_m for large n.

Test for equality

A commonly used test for equality is the logrank test in K-sample problem. The current $\mathcal{T}_{\{\cdot\}}$ can now be modified to test for equality among groups represented by different covariate values. Consider the hypotheses: H_0: $\beta_j = \gamma_j = 0, \forall j$; and H_a: at least one of β_js and γ_js is not equal to 0. The statistic ($\mathcal{T}_{\mathbf{equal}}$) evaluated at H_0 is distributed as χ^2_{2m} asymptotically. Note that the proposed test for equality can be applied under a cure model. When the cure probabilities are large for distinct groups, a genuine difference among groups could be masked (or ignored) by these large probabilities of cure. However, the proposed test may have a good power in testing the difference. In this case, it is also appealing to compare the performance of the present $\mathcal{T}$ with the 'modified' score test studied by Bagdonavicius and Nikulin (2006) under their multiple cross-effect (MCE) model.

5 Data analysis

The methods discussed above are implemented on stroke patients' survival data collected *retrospectively* from six regional teaching hospitals (bed number larger than 200) of central Taiwan during January 2002 to December 2003. This data comprises 616 individuals who experienced acute stroke with subtypes of cerebral hemorrhage, cerebral infarct or transcient ischemic attack. The zero-time point is defined as the time of an inpatient's hospitalization; and potential variables for explaining mortality rate include age, sex, disease subtype, length of hospital stay (LOS), comorbidity status of diabetes mellitus (DM) and/or hypertension, etc. Part of the patients also have Glasgow coma scale (GCS) and Barthel index data ascertained from hospital records. For a simple exposition, we only investigate the impact of 'comorbidity' on the hazards. The Kaplan-Meier (KM) survival estimates exhibit multiple crossings and a high 'cure' (or 'non-susceptible to death') probability. For the other variables, sex and LOS are not significant, age has a nonhomogeneous effect, and the hazards among different stroke subtypes satisfy proportionality. Furthermore, GCS and Barthel functional index are not recorded in a

unified manner and are missing by a large proportion. So the subsequent analysis based on HHR^{VC} is basically *univariate*. The only variable used for interpreting the mortality is 'comorbid disease status'; it is dichotomized into two groups: those *with* and *without* the coexistence of either DM or hypertension. The impact of comorbidity on the death rate of acute strokes is still inconclusive. Our analysis in this section attempts to disclose the time-varying property of relative hazards between the two groups of patients. However, the influential part of this kind of data is: There is a very high proportion of patients who still survive at the endtime of the study period.

The KM estimates are displayed in Figure 1, accompanied by a pair of survival curves obtained from the HHR^{VC} estimates. In order to give a clear comparison, the KM and HHR^{VC} survival estimates are plotted only within the range of '$t \leq 697$' with $0.85 \leq S(t) \leq 1$, because a large proportion of patients survive beyond 697 days. The estimate proposed in the current study fits well to the nonparametric KM survivals. If we denote the failure or censoring time as T, the sample are divided into four segments: those with $T < 10$, $10 \leq T < 35$, $35 \leq T < 244$ and $244 \leq T \leq 697$. The selected four segments contain 25,13,16, and 22 non-censored failure times in 25,13,16, and 562 observations. That means the first three have no right-censoring cases, and the last one has 540 censored observations. As a whole, the data has 76 failures, and censoring proportion is $540/616 = 87.7\%$. Here we don't put an artificial adjustment to get a better fit. These four segments are selected to control a balanced sample sizes between segments as well as between the two groups, so that each segment contains *no less than* 4 non-censored failures for both groups. For group 1 ('without' comorbidity) [versus group 2 ('with' comorbidity)], there are 4[21],4[9],8[8],and 5[17] failures. Table 1 reports the *point estimates* of parameters $(\alpha_j, \beta_j, \gamma_j)$ for $j = 1, 2, 3, 4$ under the HHR^{VC} model. According to this result, the rate ratio ($\widehat{\text{RR}}(t)$, for $\tau_{J-1} < t \leq \tau_J$) can be calculated from (3) and (4) as

$$\mathrm{e}^{\beta_J+\gamma_J}\{\alpha_J(t-\tau_{J-1}) + \sum_{j=1}^{J-1}\alpha_j(\tau_j - \tau_{j-1})\}^{e^{\gamma_J}-1}.$$

[Put Figure 1 about here.]

The $\mathcal{T}_{\mathbf{hetvc}}$-test for varying heteroscedasticity has a realized value of $\chi^2_3 = 44.83$ (p-value$<$ 0.001); and the $\mathcal{T}_{\mathbf{equal}}$-statistic is $\chi^2_8 = 11.72$ (p-value$=$ 0.164), indicating that the acute stroke patients' survival within 2 years is irrespective of the comorbid diseases discussed in this study and that, using HHR$^{\text{VC}}$, time-varying heteroscedasticity should be included.

Table 1: Analysis of first-ever stroke patients' two-year survivals.

Segment($j=$)	1	2	3	4	Test
α_j	3.673	0.592	0.062	0.104	$\mathcal{T}_{\mathbf{hetvc}} = 44.83 (p = 0.000)$
β_j	2.143	0.150	3.202	4.065	$\mathcal{T}_{\mathbf{equal}} = 11.72 (p = 0.164)$
γ_j	0.628	0.010	-4.751	-6.654	

6 Discussion

The results of Table 1 have some important implications. First, the baseline parameter estimates $\widehat{\alpha}$s are decreasing, revealing overall declination in the risk of death of stroke patients. This phenomenon confound with the time-varying property of β and γ. In particular, the decreasing baseline hazard and the decreasing heteroscedasticity (to a large negative value) together result in the large proportions of 'cured' patients for each group. Second, the baseline-hazard parameters modulate the overall trend of incidence of events, $\beta(t)$ reflects the relative 'location' or 'strength', and $\gamma(t)$ captures the shape or heterogeneity that interacted with time. The global validity of HHR$^{\text{VC}}$ is only diagnosed by visualized fitness in Figure 1. How to construct an omnibus (or global) test for the goodness-of-fit of the HHR$^{\text{VC}}$-model remains to be an issue.

For a regression set-up with multiple regressors, not all variables have varying effect, and not all the varying coefficients have the same 'crossing point(s)'. This involves the strategy of data analysis. Here we propose plotting Kaplan-Meier estimates for each specific covariate

after an adequate grouping. The covariates without crossings in K-M estimates are suggested not to be put in the heteroscedasticity component. For those with cross-effect, practitioners need to decide the cut-off points $\{\tau_j\}$. In practice, the selected cut-off intervals $(\tau_{j-1}, \tau_j]$ should not contain more than one crossing point. Finally, as a conclusion, we propose the application of Weibull-type regression model equipped with time-varying parameters to deal with multiple cross-effect problems, which may be combined with a cure probability.

References

Bagdonavičius, V.B. and Nikulin, M.S. (2006). Analysis of survival data with multiple crossing of survival functions. Preprint, Department of Mathematical Statistics, University of Vilnius, Lithuania and U.F.R. Sciences et modélisation, Victor Segalen Bordeaux 2 university, France.

Cox, D.R. (1972). Regression models and life-tables (with discussion). J. Roy. Statist. Soc. Ser. B. **34** 187-220.

Hougaard, P. (1986). Survival models for heterogeneous populations derived from stable distributions. *Biometrika* **73** 387-396.

Hsieh, F. (2001). On heteroscedastic hazards regression models: theory and application. *J. Roy. Statist. Soc. Ser. B* **63** 63-79.

Martinussen, T. and Scheike, T.H. (2006). *Dynamic Regression Models for Survival Data*. Springer, New York.

Marzec, L. and Marzec, P. (1997). On fitting Cox's regression model with time-dependent coefficients. *Biometrika* **84** 901-908.

Murphy, S.A. and Sen, P.K. (1991). Time-dependent coefficients in a Cox-type regression model. *Stoch. Prosess Appl.* **39**, 153-180.

Murphy, S.A. (1993). Testing for a time dependent coefficient in Cox's regression model. *Scand. J. of Statist.* **20**, 35-50.

Tien, L., Zucker, D., and Wei, L.J. (2005). On the Cox Model With Time-Varying Regression Coefficients. *J. Amer. Statist. Asso.* **100**, 172-183.

Vaupel, J.W. (1979). The Impact of Heterogeneity in Individual Frailty on the Dynamics of Mortality. *Demography* **16**, 439-454.

Valsecchi, M.G., Silvestri, D., and Sasieni, P. (1996). Evaluation of long-term survival: use of diagnostics and robust estimators with Cox's proportional hazards model. *Statist. Med.* **15** 2763-2780.

Wu, H.-D. I., Hsieh, F., Chen, C.-H. (2002). Validation of a heteroscedastic hazards regression model. *Life. Data Anal.* **8** 21-34.