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INFERENCE FOR A NONLINEAR COUNTING PROCESS REGRESSION MODEL

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Martingale and counting process techniques are applied to the problem of inference for general conditional hazard functions. This problem was first studied by Beran, who introduced a class of estimators for the conditional cumulative hazard and survival functions in the special case of time-independent covariates. Here the covariate can be time dependent; the classical i.i.d. assumptions are relaxed by replacing them with certain asymptotic stability assumptions, and models involving recurrent failures are included. This is done within the framework of a general nonparametric counting process regression model. Important examples of the model include right-censored survival data, semi-Markov processes, an illness–death process with duration dependence, and age-dependent birth and death processes.

1. Introduction. Suppose that the conditional hazard function

$$\lambda(t|Z_i) = \lim_{\varepsilon \downarrow 0} \frac{1}{\varepsilon} P(T_i \le t + \varepsilon | T_i > t; Z_i(s), s \le t)$$

for the survival time T_i of an individual with covariate process $Z_i = (Z_i(t))$ has the form

$$\lambda(t|Z_i) = \alpha(t, Z_i(t)), \qquad i = 1, \dots, n, \tag{1.1}$$

where α is a completely general function of time t and the state of the covariate process at time t. Inference for this fully nonparametric model was initiated by Beran (1981), who introduced a class of estimators for the conditional cumulative hazard and survival functions, $A(\cdot, z) = \int_0 \alpha(s, z)\, ds$ and $S(\cdot, z) = e^{-A(\cdot, z)}$, respectively, in the special case that the covariate Z is not time dependent. Weak convergence results for Beran's estimators have been obtained by Dabrowska (1987) using a conditional version of the classical approach to Breslow and Crowley (1974).

The purpose of the present paper is to show that martingale and counting process techniques, known to be powerful tools in survival analysis since the work of Aalen (1975, 1978), can also be applied successfully in the setting described above. There are many advantages to this approach: much simpler proofs can be given; more general censoring patterns can be allowed; the

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covariate can be time dependent (the only restriction being that it is a predictable process); the classical i.i.d. assumptions can be relaxed by replacing them with certain asymptotic stability assumptions; and models involving recurrent failures are naturally included in the analysis by allowing the counting processes to have more than one jump. In addition, the martingale approach suggests and makes possible an elaborate statistical theory centered on the conditional cumulative hazard function and the doubly cumulative hazard function $\mathscr{A}(t,z) = \int_0^z \int_0^t \alpha(s,x)\,ds\,dx$. It is natural to estimate $\mathscr{A}(t,z)$ by integrating Beran's estimator, denoted $\hat{A}(t,x)$, over the covariate state space to obtain

$$\hat{\mathscr{A}}(t,z) = \int_0^z \hat{A}(t,x)\,dx. \tag{1.2}$$

In subsequent work, based on the approach developed in the present paper, we shall establish a weak convergence result for $\hat{\mathscr{A}}$ which leads to some new goodness-of-fit tests for various important submodels of (1.1) (e.g., Cox's proportional hazards model), see McKeague and Utikal (1988, 1990a, 1990b).

The counting process formulation of the model (1.1) and several important examples are described in Section 2. Estimators for $A(\cdot,z)$, $S(\cdot,z)$ and α are introduced and their asymptotic properties are stated under various general conditions in Section 3. In Section 4 we check that these conditions are satisfied for the i.i.d. case. All proofs are contained in Section 5.

2. Model formulation and examples. Let $\mathbf{N}(t) = (N_1(t),\dots,N_n(t))'$, $t \in [0,1]$, be a multivariate counting process with respect to a right-continuous filtration $(\mathscr{F}_t^{(n)})$, i.e., $\mathbf{N}$ is adapted to the filtration and has components N_i which are right-continuous step functions, zero at time zero, with jumps of size $+1$ such that no two components jump simultaneously. Here $N_i(t)$ records the number of observed failures for the ith individual during the interval $[0,t]$ over the whole study period (taken to be $[0,1]$). Suppose that N_i has intensity

$$\lambda_i(t) = Y_i(t)\alpha(t, Z_i(t)), \qquad i = 1,\dots,n, \tag{2.1}$$

i.e., $M_i(t) = N_i(t) - \int_0^t \lambda_i(s)\,ds$ is a local martingale, where $Y_i(t)$ is a predictable $\{0,1\}$-valued process, indicating that the ith individual is at risk when $Y_i(t) = 1$, and $Z_i(t)$ is a predictable covariate process.

The problem is to carry out inference, based on observation of (N_i, Y_i, Z_i), $i = 1,\dots,n$, for α over some given region in the (t,z)-plane. In fact, rather than observing the whole covariate process Z_i, it is sufficient to observe Z_i at times when the individual is at risk [i.e., when $Y_i(t) = 1$]. To be specific, the region of inference is taken to be the unit square $[0,1]^2$. Note that α may vanish over part of this region, as in Example 3. Some useful examples of model (2.1) follow.

EXAMPLE 1 (Right-censored survival data). The observable portion of an individual's lifetime T is given by $\tilde{T} = \min(T, C)$, where C is the censoring time. Suppose that T and C are conditionally independent given a left-continuous covariate process Z, and suppose that the conditional hazard of T given $(Z(s),\ s \le t)$ is $\alpha(t, Z(t))$. For each of n independent copies (T_i, C_i, Z_i), $i = 1, \dots, n$ of (T, C, Z), we observe $\tilde{T}_i$, $\delta_i = I(T_i \le C_i)$ and $Z_i(t)$ for $t \le \tilde{T}_i$. Let $N_i(t) = I(\tilde{T}_i \le t,\ \delta_i = 1)$ be the counting process with a single jump at an uncensored survival time. Then $\mathbf{N}(t) = (N_1(t), \dots, N_n(t))'$ is a multivariate counting process and N_i has intensity (2.1), where $Y_i(t) = I(\tilde{T}_i \ge t)$ is the indicator that the individual is observed to be at risk at time t.

Example 2 (A non-Markovian pure jump process). Consider a pure jump process $(X(t))$ describing the motion of a particle on a finite state space. Suppose that the intensity $\alpha_{jk}(t, z)$ of transition from state j to state k depends on clock time t and on the time z spent in state j since the last jump. Then the counting process $N_{jk}(t)$ which registers the number of transitions from state j to state k up to time t has intensity $\lambda_{jk}(t) = Y_j(t)\alpha_{jk}(t, L(t))$, where $Y_j(t) = I(X(t-) = j)$ is the indicator that the particle is in state j at time $t-$, and $L(t)$ is length of time at $t-$ which has elapsed since the last jump. In the terminology of Markov renewal processes (Pyke, 1961), $L(t)$ is the backward recurrence time. Let V denote the (clock) time of the last jump prior to $t = 0$. The data needed to estimate α_{jk} consist of n copies $(N_{ijk}(t), Y_{ij}(t),\ t \in [0,1],\ V_i)$, $i = 1, \dots, n$ of $(N_{jk}(t), Y_j(t),\ t \in [0,1],\ V)$, with $\mathbf{N}_{jk}(t) = (N_{1jk}(t), \dots, N_{njk}(t))'$ required to be a multivariate counting process. Right censoring can be introduced into this example as well [see, e.g., Andersen, Borgan, Gill and Keiding (1988), Section 3].

If each transition intensity $\alpha_{jk}(t, z)$ only depends on the clock time t, then X is a Markov process for which inference has been studied by Aalen and Johansen (1978). When each $\alpha_{jk}(t, z)$ only depends on the backward recurrence time, then X is a semi-Markov or Markov renewal process for which inference has been studied by Gill (1980) [cf. Sellke and Siegmund (1983) and Slud (1984)]. In McKeague and Utikal (1988a) we develop goodness-of-fit tests for the Markov and semi-Markov submodels within the general model (2.1), utilizing the doubly cumulative hazard function estimator $\hat{\mathscr{A}}$ mentioned in the introduction.

Example 3 (An illness–death process with duration dependence). As a special case of Example 2, consider an individual who can be in any one of three states: healthy, diseased or dead—denoted 0, 1 and 2, respectively. The clock time t is the age of the individual. The individual starts in state 0 at $t = 0$ (so $V \equiv 0$) and subsequently makes transitions $0 \to 1 \to 2$ or $0 \to 2$. The incidence rate of the disease, $\alpha_{01}(t)$, and the mortality rate of the healthy, $\alpha_{02}(t)$, depend only on age t. However, the mortality rate of the diseased, $\alpha_{12}(t, z)$, depends on both age t and the duration of the illness z.

This type of model has been of interest in epidemiology at least since the work of Fix and Neyman (1951) [cf. Chiang (1980)]; recent discussion of the model may be found in Keiding (1990) and Andersen, Borgan, Gill and Keiding (1988). Note that the mortality rate of the diseased, $\alpha_{12}(t,z)$, vanishes for $z \geq t$, so it is only necessary to estimate $\alpha_{12}(t,z)$ in the triangle $\{(t,z) \in [0,1]^2 : z < t\}$.

EXAMPLE 4 (Age-dependent birth and death process). This example is another special case of Example 2. Suppose that there are three states, 0, 1 and 2, with possible transitions $0 \to 1 \to 2$. Under the interpretation $1 =$ alive and $2 =$ dead, $t =$ calendar time and $z =$ the age of the individual, $\alpha_{12}(t,z)$ is the calendar time $\times$ age-specific mortality rate. If the individual is alive at $t = 0$, then $V =$ date of birth.

This type of process, as well as an age-dependent birth process, was first studied by Kendall (1949) in the case of individuals having calendar time independent birth and death rates. Recently, Keiding, Holst and Green (1989) applied the model to the estimation of the calendar time $\times$ age-specific diabetes incidence rate among the inhabitants of Fyn county, Denmark. Keiding, Holst and Green remark that the possibility of estimating calendar time $\times$ age-specific intensities nonparametrically seems to be new, except that Capasso (1988) has outlined some basic relevant martingales and suggested estimates of piecewise constant intensities.

3. The estimators and their asymptotic properties. We begin this section by giving the notation used to define our versions of Beran's (1981) estimators for the cumulative conditional hazard function $A(t,z)$ and the conditional survival function $S(t,z)$. For fixed z, let $N_i(t,z)$ be the counting process which registers the jumps of $N_i(t)$ when $Z_i(t) \in \mathscr{I}_z$, where $\mathscr{I}_z \subset [0,1]$ is an interval of length w_n containing z, so that $N_i(t,z) = \int_0^t I\{Z_i(s) \in \mathscr{I}_z\}\, dN_i(s)$, and let $N^{(n)}(s,z) = \sum_{i=1}^n N_i(s,z)$ denote the aggregated counting process. Set

$$Y^{(n)}(s,z) = \sum_{i=1}^{n} I\{Z_i(s) \in \mathscr{I}_z\} Y_i(s),$$

the size of the risk set of individuals with covariate in $\mathscr{I}_z$ at risk at time s. In Example 4, for instance, $Y^{(n)}(s,z)$ is the size of the cohort of individuals born in the calendar time interval $s - \mathscr{I}_z$ and observed to be alive at time s. Note that $\mathscr{I}_z$ depends implicitly on n.

Beran's estimators are defined as the Nelson–Aalen and product-limit type estimators,

$$\hat{A}(t,z) = \int_0^t \frac{N^{(n)}(ds,z)}{Y^{(n)}(s,z)},$$

$$\hat{S}(t,z) = \prod_{s \leq t} \left(1 - \Delta \hat{A}(s,z)\right),$$

respectively, where $\Delta \hat{A}(s,z) = \hat{A}(s,z) - \hat{A}(s-,z)$, and by convention $1/0 \equiv 0$ (this convention is adopted throughout the paper). The bin width w_n should tend to zero at a suitable rate as $n \to \infty$. By smoothing $\hat{A}(ds, z)$ we can estimate $\alpha(t, z)$ itself [cf. Ramlau-Hansen (1983)]. For $t \in (0, 1)$, set

$$\hat{\alpha}(t, z) = \frac{1}{b_n} \int_0^1 K\left(\frac{t - s}{b_n}\right) \hat{A}(ds, z),$$

where K is a bounded, nonnegative kernel function with support $[-1, 1]$, integral 1 and $b_n > 0$ is a bandwidth parameter, $b_n \to 0$.

We may regard the preceding estimators as being defined for all $z \in [0, 1]$ by stratifying over z: Take a partition $\mathscr{I}_r$, $r = 1, \ldots, d_n$, of $[0, 1]$ into intervals of length $w_n = 1/d_n$ say, where d_n is an increasing sequence of positive integers, and set $\mathscr{I}_z = \mathscr{I}_r$ when $z \in \mathscr{I}_r$. Then the estimator $\hat{\mathscr{A}}$ given by (1.2) is fully defined. It is possible to show that $\hat{\alpha}(\cdot, z)$ is a uniformly consistent estimator of $\alpha(\cdot, z)$ for each fixed z. However, by smoothing $\hat{\alpha}$ in the z direction, we obtain what turns out to be a uniformly consistent estimator of the whole function α:

$$\tilde{\alpha}(t, z) = \frac{1}{\tilde{b}_n} \int_0^1 \tilde{K}\left(\frac{z - x}{\tilde{b}_n}\right) \hat{\alpha}(t, x)\, dx,$$

where $\tilde{K}$ is a kernel function and $\tilde{b}_n$ is a bandwidth parameter; $\tilde{K}$ and $\tilde{b}_n$ having the same properties as K and b_n. A similar estimator has been used by Keiding, Holst and Green (1988) in the context of Example 4 to obtain three-dimensional visualizations of diabetes incidence rates plotted against onset year and onset age. An essentially equivalent way to define $\tilde{\alpha}$, as is apparent from the Proof of Theorem 4, would be to doubly smooth $\hat{\mathscr{A}}(ds, dz)$ over both s and z in the fashion of Ramlau-Hansen (1983).

We now proceed to state the main results of the paper. It is assumed throughout that α is Lipschitz on its support, $\mathrm{supp}(\alpha) = \{(s, z)\colon \alpha(s, z) > 0\}$. The following condition is needed for Theorems 1 and 2 which give the asymptotic distributions of $\hat{A}(\cdot, z)$ and $\hat{S}(\cdot, z)$. We need some notation (in which the presence of n is implicit):

$$\mathscr{T}_z = \{s \in [0, 1]\colon \mathscr{I}_z \text{ is contained in the support of } \alpha(s, \cdot)\},$$

$$\overline{\mathscr{T}_z} = \{s \in [0, 1]\colon \alpha(s, u) > 0 \text{ and } \alpha(s, v) = 0 \text{ for some } u, v \in \mathscr{I}_z\}.$$

CONDITION A.

(A1) For fixed z there exists a nonnegative bounded measurable function $g(\cdot, z)$ defined on the support of $\alpha(\cdot, z)$ such that

$$\int_{\mathscr{T}_z} \left| \frac{nw_n}{Y^{(n)}(s, z)} - g(s, z) \right| ds \to_P 0.$$

(A2) $\mathrm{Leb}\{s \in \mathscr{T}_z\colon Y^{(n)}(s, z) = 0\} = o_P(1/\sqrt{nw_n})$.
(A3) $\mathrm{Leb}(\overline{\mathscr{T}_z}) = O(w_n)$.

Condition (A1) is an asymptotic stability condition on the normalized size of the risk set. In Example 4, for instance, $Y^{(n)}(s, z)/nw_n$ estimates the "density" of the cohort of individuals born at calendar time $s - z$ and observed to be alive at time s, so it is reasonable to require that this quantity satisfy *some* sort of asymptotic stability condition [cf. condition (4.13) of Capasso (1988)]. Condition (A2) controls the amount of time (expressed formally in terms of Lebesgue measure) that the risk set can be empty.

Condition (A3) is a mild regularity assumption on the boundary of supp(α) used to control an "edge effect" that arises there. It is satisfied for the illness–death model in Example 3, for instance, since for that example supp(α) is the triangle $\{(t, z) \in [0, 1]^2 \colon z < t\}$, so $\overline{\mathscr{T}_z} = \mathscr{I}_z$ which has Lebesgue measure w_n.

Let $h(t, z) = \alpha(t, z) g(t, z)$ if $(t, z) \in \text{supp}(\alpha)$, zero otherwise.

THEOREM 1. *If Condition* A *holds*, $nw_n \to \infty$ *and* $nw_n^2 \to 0$, *then*

$$\sqrt{nw_n}\left(\hat{A}(\cdot, z) - A(\cdot, z)\right) \to_{\mathscr{D}} U(\cdot, z)$$

in $D[0,1]$, *where* $U(\cdot, z)$ *is a continuous Gaussian martingale with zero mean and variance function*

$$\text{Var}(U(t, z)) = \int_0^t h(s, z)\, ds.$$

THEOREM 2. *Under the hypotheses of Theorem* 1,

$$\sqrt{nw_n}\left(\hat{S}(\cdot, z) - S(\cdot, z)\right) \to_{\mathscr{D}} S(\cdot, z) U(\cdot, z)$$

in $D[0,1]$, *where* $U(\cdot, z)$ *is the continuous Gaussian martingale of Theorem* 1.

Theorems 1 and 2 can be used to derive confidence bands for the conditional cumulative hazard and conditional survival functions, just as in the unconditional case [see Andersen and Borgan (1985), page 114 and Hall and Wellner (1980)]. To construct such bands, we would first need to estimate the function $H(\cdot, z) = \int_0^{\cdot} h(s, z)\, ds$. It can be shown that

$$\hat{H}(\cdot, z) = nw_n \int_0^{\cdot} \frac{N^{(n)}(ds, z)}{\left(Y^{(n)}(s, z)\right)^2}$$

is a uniformly consistent estimator of $H(\cdot, z)$ suitable for that purpose [see McKeague and Utikal (1987)].

It is possible to extend Theorem 1 to deal with a finite set of distinct covariate levels $z_1, \dots, z_p$. The asymptotic joint distribution of the normalized $(\hat{A}(\cdot, z_j))_{j=1}^p$ is a p-variate Gaussian martingale having orthogonal (thus independent) components $U(\cdot, z_j)$. The key ingredient here is that the aggregated counting processes $N^{(n)}(\cdot, z_j)$ have no common jumps when the intervals $\mathscr{I}_{z_j}$ are disjoint, as is the case when w_n is small enough. Thus the martingale parts of these counting processes are asymptotically orthogonal, leading via the martingale central limit theorem to asymptotic independence of the $\hat{A}(\cdot, z_j)$.

Note that the $U(\cdot, z_j)$ can be represented as stochastic integrals $\int_0^{\cdot}\sqrt{h(s, z_j)}\, dW_j(s)$, where $W_1, \dots, W_p$ are independent standard Wiener processes. Summing over j we obtain an approximation to the asymptotic distribution of the doubly cumulative hazard function estimator $\hat{\mathscr{A}}$. Indeed, it can be shown that

$$\sqrt{n}\,(\hat{\mathscr{A}} - \mathscr{A}) \to_{\mathscr{D}} \int_0^{\cdot}\int_0^{\cdot}\sqrt{h(s,x)}\, dW(s,x),$$

where W is a standard Wiener field on $[0,1]^2$ [see McKeague and Utikal (1990a)].

We shall use the following condition, having an interpretation similar to Condition A, to obtain an asymptotic distribution result for $\hat{\alpha}(t, z)$.

CONDITION B.

(B1) For fixed (t, z), $0 < t < 1$, there exists a bounded measurable function $g(\cdot, z)$, which is continuous at t and defined in a neighborhood of t, such that

$$\int_{t-b_n}^{t+b_n}\left|\frac{nw_n}{Y^{(n)}(s,z)} - g(s,z)\right| ds = o_P(b_n).$$

(B2) $\mathrm{Leb}\{s \in [t - b_n, t + b_n]\colon Y^{(n)}(s, z) = 0\} = o_P(1/\sqrt{n})$.

THEOREM 3. *Suppose that Condition* B *holds for a fixed* (t, z), $0 < t < 1$, *such that* $\alpha(t, z) > 0$. *If* $b_n \sim w_n$, $nw_n^2 \to \infty$ *and* $nw_n^4 \to 0$, *then*

$$\sqrt{nw_n^2}\,(\hat{\alpha}(t,z) - \alpha(t,z)) \to_{\mathscr{D}} N(0, \sigma^2(t,z)),$$

where

$$\sigma^2(t,z) = h(t,z)\int_{-1}^{1} K^2(u)\, du.$$

Pointwise confidence intervals for $\alpha(t, z)$ can be obtained from Theorem 3 using

$$\hat{h}(t,z) = \frac{1}{b_n}\int_0^1 K\left(\frac{t-s}{b_n}\right)\hat{H}(ds, z)$$

to estimate $h(t, z)$, where K is the same kernel function used to define $\hat{\alpha}(t, z)$; see McKeague and Utikal (1987) for a proof that $\hat{h}$ is a consistent estimator of h.

The following condition is needed to prove the uniform consistency of $\tilde{\alpha}$. With n implicit, denote

$$\mathscr{T} = \{(s,z) \in [0,1]^2\colon \mathscr{I}_z \text{ is contained in the support of } \alpha(s,\cdot)\},$$

$$\overline{\mathscr{T}} = \{(s,z) \in [0,1]^2\colon \alpha(s,u) > 0 \text{ and } \alpha(s,v) = 0 \text{ for some } u, v \in \mathscr{I}_z\}.$$

CONDITION C.

(C1) $E\iint_{\mathscr{T}} nw_n/[Y^{(n)}(s,x)]\,ds\,dx = O(1)$.
(C2) $\text{Leb}_2\{(s,x) \in \mathscr{T}\colon Y^{(n)}(s,x) = 0\} = o_P(b_n \tilde{b}_n)$.
(C3) $\text{Leb}_2(\overline{\mathscr{T}}) = O(w_n)$.

Condition (C3) is similar to Condition (A3). It is satisfied for the illness–death model since $\overline{\mathscr{T}} = \bigcup_{r=1}^{d_n} \mathscr{I}_r \times \mathscr{I}_r$, which has two-dimensional Lebesgue measure w_n.

THEOREM 4. *Suppose that* $EN_i(1) < \infty$ *for each* $i \geq 1$, *Condition* C *holds*, K *and* $\tilde{K}$ *are left-continuous and of bounded variation*, $nw_n b_n^2 \tilde{b}_n^2 \to \infty$ *and* $w_n = o(b_n \tilde{b}_n)^2$ (*e.g.*, $w_n \sim n^{-1/2}$ *and* $b_n = \tilde{b}_n \sim n^{-1/9}$). *If* $0 < t_1 < t_2 < 1$ *and* $0 < z_1 < z_2 < 1$, *then*

$$\sup_{t \in [t_1, t_2]} \sup_{z \in [z_1, z_2]} |\tilde{\alpha}(t,z) - \alpha(t,z)| \to_P 0.$$

It is worth noting that the estimators and results of this section can be extended to deal with the analogous inference problem for continuous semimartingales and, in particular, *diffusion processes*, for which α is the *drift* of the diffusion. Indeed, suppose that N_i is a continuous semimartingale having canonical decomposition of the form $N_i(t) = \int_0^t \lambda_i(s)\,ds + M_i(t)$, where λ_i satisfies (2.1) and M_i, $i = 1, \dots, n$, are orthogonal square integrable martingales. If the predictable quadratic variation process of M_i has the form $\langle M_i \rangle(t) = \int_0^t \gamma(s, Z_i(s), Y_i(s))\,ds$, where γ is a bounded and measurable function, and we define $h(t,z) = \gamma(t,z,1)g(t,z)$, then Theorems 1–4 continue to hold precisely as stated. In the diffusion process case $Y_i \equiv 1$, the covariate process is the diffusion process itself, and γ is the infinitesimal variance.

4. The i.i.d. case. We have seen that the mild conditions (A3) and (C3) are satisfied for the illness–death model. In this section we show that the remaining parts of Conditions A, B and C hold in the i.i.d. case in which (N_i, Y_i, Z_i), $i \geq 1$, are independent copies of some generic triple (N, Y, Z), and for the illness–death model in particular. Let the subdistribution function of the state of the covariate process at time s when $Y(s) = 1$ be denoted $F(s, \cdot)$, i.e., $F(s,x) = P(Z(s) \leq x, Y(s) = 1)$, $-\infty < x < \infty$.

PROPOSITION 1 (i.i.d. case). *Suppose that for each* $s \in [0,1]$, $F(s, \cdot)$ *is absolutely continuous on the support of* $\alpha(s, \cdot)$ *in* $[0,1]$ *and has density* $f(s, \cdot)$ *such that* $f(\cdot, \cdot)$ *is continuous and bounded away from zero on* $\text{supp}(\alpha)$. *Define*

$$g(s,z) = 1/f(s,z) \quad \textit{for } (s,z) \in \text{supp}(\alpha).$$

With this choice of g:

(i) *If $nw_n \to \infty$, then Conditions* (A1) *and* (A2) *hold.*

(ii) *If $nw_n \to \infty$ and $b_n \sim w_n$, then Condition* B *holds for each $(t, z) \in$* supp(α).

(iii) *If $nw_n b_n^2 \tilde{b}_n^2 \to \infty$, then Conditions* (C1) *and* (C2) *hold.*

In Proposition 1 the assumption concerning the density of $F(s, \cdot\,)$ is stronger than necessary for parts (i) and (ii) since we really only need such an assumption holding in the part of some neighborhood of z contained in [0, 1], and for (ii) we only need it in some neighborhood of $t \in (0, 1)$.

EXAMPLE 5 (The illness–death process). To check the hypotheses of Proposition 1 for the illness–death model defined in Example 3, note that f is given by

$$f(s, z) = \left\{\exp\left[-\int_{s-z}^{s} \alpha_{12}(v, v - s + z)\, dv\right]\right\}\alpha_{01}(s - z)$$
$$\exp\left[-\int_0^{s-z} \alpha_{01}(u)\, du\right]$$

for $0 \le z < s \le 1$, zero otherwise. If α_{01} is continuous and bounded away from zero, then the hypotheses of Proposition 1 are satisfied.

5. Proofs.

PROOF OF THEOREM 1. Define the processes

$$M^{(n)}(t, z) = \sum_{i=1}^{n} \int_0^t I\{Z_i(s) \in \mathscr{I}_z\}\, dM_i(s),$$
$$\alpha^{(n)}(t, z) = \sum_{i=1}^{n} I\{Z_i(t) \in \mathscr{I}_z\} Y_i(t) \alpha(t, Z_i(t)),$$

so that by (2.1),

$$\sqrt{nw_n}\,(\hat{A}(t, z) - A(t, z)) = X^{(n)}(t) + R^{(n)}(t),$$

where

$$X^{(n)}(t) = \sqrt{nw_n} \int_0^t \frac{M^{(n)}(ds, z)}{Y^{(n)}(s, z)},$$
$$R^{(n)}(t) = \sqrt{nw_n} \int_0^t \left[\frac{\alpha^{(n)}(s, z)}{Y^{(n)}(s, z)} - \alpha(s, z)\right] ds.$$

Note that, since α is bounded, $\alpha^{(n)}(s, z) \le O(1) Y^{(n)}(s, z)$ uniformly in s, z and $\omega \in \Omega$. Also, since α is assumed to be Lipschitz on its support,

$$\alpha^{(n)}(s, z) = (\alpha(s, z) + O(w_n)) Y^{(n)}(s, z), \tag{5.1}$$

uniformly for $s \in \mathscr{T}_z$ and $\omega \in \Omega$. This formula will be used repeatedly. In particular, since $\alpha(\cdot, z)$ and $\alpha^{(n)}(\cdot, z)$ vanish outside $\mathscr{T}_z \cup \overline{\mathscr{T}_z}$,

$$\begin{aligned}\sup_t |R^{(n)}(t)| &\le \sqrt{nw_n}\int_{\mathscr{T}_z}\left|\frac{(\alpha(s,z)+O(w_n))Y^{(n)}(s,z)}{Y^{(n)}(s,z)} - \alpha(s,z)\right| ds \\ &\quad + O\left(\sqrt{nw_n}\right)\mathrm{Leb}\left(\overline{\mathscr{T}_z}\right) \\ &= O\left(\sqrt{nw_n}\right)\mathrm{Leb}\{s \in \mathscr{T}_z : Y^{(n)}(s,z) = 0\} + O\left(\sqrt{nw_n^3}\right) \to_P 0,\end{aligned}$$

by (A2), (A3) and $nw_n^2 \to 0$. Note that the stochastic integral $X^{(n)}$ is a local square integrable martingale with respect to $(\mathscr{F}_t^{(n)})$. We shall apply the version of Rebolledo's (1980) martingale central limit theorem stated in Andersen and Gill (1982). The predictable variation of $X^{(n)}$ is

$$\begin{aligned}\langle X^{(n)}\rangle_t &= nw_n\int_0^t \frac{\alpha^{(n)}(s,z)}{\left(Y^{(n)}(s,z)\right)^2}\, ds \\ &= nw_n\int_0^t \frac{(\alpha(s,z)+O(w_n))}{Y^{(n)}(s,z)} I(s \in \mathscr{T}_z)\, ds + O(nw_n)\mathrm{Leb}\left(\overline{\mathscr{T}_z}\right),\end{aligned}$$

by (5.1), so that

$$\begin{aligned}&\left|\langle X^{(n)}\rangle_t - \int_0^t g(s,z)\alpha(s,z)\, ds\right| \\ &\quad \le O(1)\int_{\mathscr{T}_z}\left|\frac{nw_n}{Y^{(n)}(s,z)} - g(s,z)\right| ds + O(nw_n)\mathrm{Leb}\left(\overline{\mathscr{T}_z}\right) \to_P 0,\end{aligned}$$

by (A1), (A3) and $nw_n^2 \to 0$. Next we check the Lindeberg condition

$$L_n = nw_n\int_0^1 \frac{\alpha^{(n)}(s,z)}{\left(Y^{(n)}(s,z)\right)^2} I\left\{\frac{\sqrt{nw_n}}{Y^{(n)}(s,z)} > \varepsilon\right\} ds \to_P 0,$$

for all $\varepsilon > 0$. Using Conditions (A1) and (A3) as before,

$$L_n = O(1)\mathrm{Leb}\left\{s \in \mathscr{T}_z : \frac{\sqrt{nw_n}}{Y^{(n)}(s,z)} > \varepsilon\right\} + O\left(nw_n^2\right) + o_P(1).$$

The Lebesgue term may be written

$$\begin{aligned}&\mathrm{Leb}\left\{s \in \mathscr{T}_z : \frac{nw_n}{Y^{(n)}(s,z)} > \varepsilon\sqrt{nw_n}\right\} \\ &\quad \le \mathrm{Leb}\left\{s \in \mathscr{T}_z : \left|\frac{nw_n}{Y^{(n)}(s,z)} - g(s,z)\right| > \varepsilon\sqrt{nw_n} - \sup_{t \in \mathscr{T}_z} g(t,z)\right\} \\ &\quad \le \mathrm{Leb}\left\{s \in \mathscr{T}_z : \left|\frac{nw_n}{Y^{(n)}(s,z)} - g(s,z)\right| > \frac{\varepsilon}{2}\sqrt{nw_n}\right\} \\ &\quad \le \frac{2}{\varepsilon\sqrt{nw_n}}\int_{\mathscr{T}_z}\left|\frac{nw_n}{Y^{(n)}(s,z)} - g(s,z)\right| ds \\ &\quad = o_P\left(\frac{1}{\sqrt{nw_n}}\right),\end{aligned}$$

where the second to last inequality holds for n sufficiently large since $nw_n \to \infty$, and we have used (A1) to obtain the last line. □

PROOF OF THEOREM 2. The proof is omitted since it closely follows Gill's (1983) derivation of the asymptotic distribution of the product-limit estimator in the unconditional case, except that $\sqrt{n}$ is replaced by $\sqrt{nw_n}$. An alternative proof can be given by making direct use of Theorem 1, the Hadamard differentiability of the product integral (Gill and Johansen, 1990), and applying a functional version of the delta method (Gill, 1989). □

PROOF OF THEOREM 3. Note that

$$\sqrt{nw_n^2}\,(\hat{\alpha}(t,z) - \alpha(t,z)) = X^{(n)}(1) + R^{(n)},$$

where (defining $X^{(n)}$ and $R^{(n)}$ differently from the Proof of Theorem 1)

$$X^{(n)}(\tau) = \sqrt{nw_n^2}\,\frac{1}{b_n}\int_0^\tau K\left(\frac{t-s}{b_n}\right)\frac{1}{Y^{(n)}(s,z)}M^{(n)}(ds,z),$$

$$R^{(n)} = \sqrt{nw_n^2}\left[\frac{1}{b_n}\int_0^1 K\left(\frac{t-s}{b_n}\right)\frac{\alpha^{(n)}(s,z)}{Y^{(n)}(s,z)}\,ds - \alpha(t,z)\right].$$

We shall apply Rebolledo's martingale central limit theorem to the local square integrable martingale $X^{(n)}$. The predictable variation of $X^{(n)}$ at $\tau = 1$ is

$$\langle X^{(n)}\rangle_1 = \frac{nw_n}{b_n}\int_0^1 K^2\left(\frac{t-s}{b_n}\right)\frac{\alpha^{(n)}(s,z)}{\left(Y^{(n)}(s,z)\right)^2}\,ds.$$

Consider the r.h.s. of the inequality

$$\left|\langle X^{(n)}\rangle_1 - \sigma^2(t,z)\right| \le \left|\langle X^{(n)}\rangle_1 - \frac{1}{b_n}\int_0^1 K^2\left(\frac{t-s}{b_n}\right)h(s,z)\,ds\right| + \left|\frac{1}{b_n}\int_0^1 K^2\left(\frac{t-s}{b_n}\right)h(s,z)\,ds - \sigma^2(t,z)\right|.$$

Continuity of $g(\cdot,z)$ and $\alpha(\cdot,z)$ at t implies that the second term tends to zero. By (5.1) the first term is bounded above by

$$O(1)\frac{1}{b_n}\int_0^1 K^2\left(\frac{t-s}{b_n}\right)\left|\frac{nw_n}{Y^{(n)}(s,z)} - g(s,z)\right|ds + O(w_n)\frac{1}{b_n}\int_0^1 K^2\left(\frac{t-s}{b_n}\right)g(s,z)\,ds,$$

which tends to zero in probability by Condition (B1). Thus $\langle X^{(n)}\rangle_1 \to_P \sigma^2(t,z)$. We also need to check the Lindeberg condition

$$L_n = \frac{nw_n^2}{b_n^2}\int_0^1 K^2\left(\frac{t-s}{b_n}\right)\frac{\alpha^{(n)}(s,z)}{\left(Y^{(n)}(s,z)\right)^2} I\left\{K\left(\frac{t-s}{b_n}\right)\frac{\sqrt{nw_n^2}/b_n}{Y^{(n)}(s,z)} > \varepsilon\right\}ds \to_P 0,$$

for all $\varepsilon > 0$. Using (5.1) again, we have that, for some $\varepsilon' > 0$,

$$L_n \le \frac{O(1)}{b_n}\int_0^1 K^2\left(\frac{t-s}{b_n}\right)\frac{nw_n}{Y^{(n)}(s,z)} I\left\{K\left(\frac{t-s}{b_n}\right)\frac{\sqrt{n}}{Y^{(n)}(s,z)} > \varepsilon'\right\} ds$$

$$\le \frac{O(1)}{b_n}\int_0^1 K^2\left(\frac{t-s}{b_n}\right)\left|\frac{nw_n}{Y^{(n)}(s,z)} - g(s,z)\right| ds$$

$$+ \frac{O(1)}{b_n}\operatorname{Leb}\left\{s \in [t-b_n, t+b_n]: \frac{\sqrt{n}}{Y^{(n)}(s,z)} > \varepsilon'\right\}.$$

The first term tends in probability to zero by (B1). Using the same argument employed to deal with the Lebesgue term in the Proof of Theorem 1, except now restricted to the interval $[t-b_n, t+b_n]$, we see that the second term is of order $o_P(1/\sqrt{n}\,w_n)$. Finally, using (5.1) again,

$$R^{(n)} = O\left(\sqrt{nw_n^4}\right) + \sqrt{nw_n^2}\left[\frac{1}{b_n}\int_0^1 K\left(\frac{t-s}{b_n}\right)\alpha(s,z)\,ds - \alpha(t,z)\right]$$

$$-\sqrt{nw_n^2}\,\frac{1}{b_n}\int_0^1 K\left(\frac{t-s}{b_n}\right) I\{s: Y^{(n)}(s,z) = 0\}\alpha(s,z)\,ds.$$

The second term here tends to zero by the Lipschitz condition on α, and the last term tends to zero in probability by Condition (B2). □

Proof of Theorem 4. It is easily shown, using integration by parts, Fubini's theorem and the assumptions of α Lipschitz and $K, \tilde{K}$ left-continuous with bounded support and bounded variation, that

$$\alpha(t,z) = \frac{1}{b_n\tilde{b}_n}\int_0^1\int_0^1 \mathscr{A}(s,x)\,d\tilde{K}\left(\frac{z-x}{\tilde{b}_n}\right)dK\left(\frac{t-s}{b_n}\right) + o(1)$$

$$\tilde{\alpha}(t,z) = \frac{1}{b_n\tilde{b}_n}\int_0^1\int_0^1 \hat{\mathscr{A}}(s,x)\,d\tilde{K}\left(\frac{z-x}{\tilde{b}_n}\right)dK\left(\frac{t-s}{b_n}\right) + o_P(1)$$

uniformly over $(t,z) \in [t_1,t_2]\times[z_1,z_2]$ as $n \to \infty$. In the same sense we have

$$\tilde{\alpha}(t,z) - \alpha(t,z)$$

$$= \frac{1}{b_n\tilde{b}_n}\int_0^1\int_0^1\int_0^x (\hat{A} - A)(s,u)\,du\,d\tilde{K}\left(\frac{z-x}{\tilde{b}_n}\right)dK\left(\frac{t-s}{b_n}\right) + o_P(1)$$

$$= \frac{1}{b_n\tilde{b}_n}\int_0^1\int_0^1\int_0^x\int_0^s \frac{M^{(n)}(dv,u)}{Y^{(n)}(v,u)}\,du\,d\tilde{K}\left(\frac{z-x}{\tilde{b}_n}\right)dK\left(\frac{t-s}{b_n}\right) + o_P(1)$$

$$+ \frac{1}{b_n\tilde{b}_n}\int_0^1\int_0^1\int_0^x\int_0^s\left[\frac{\alpha^{(n)}(v,u)}{Y^{(n)}(v,u)} - \alpha(v,u)\right]$$

$$dv\,du\,d\tilde{K}\left(\frac{z-x}{\tilde{b}_n}\right)dK\left(\frac{t-s}{b_n}\right).$$

Using Conditions (C2) and (C3), (5.1) and $w_n = o(b_n \tilde{b}_n)$, the last term above is seen to be of order $o_P(1)$, cf. the treatment of $R^{(n)}(t)$ in the Proof of Theorem 1. The expectation of the supremum over $(t, z) \in [0, 1]^2$ of the absolute value of the first term is bounded above by

$$\frac{O(1)}{b_n \tilde{b}_n} \int_0^1 E \sup_s \left| \int_0^s \frac{M^{(n)}(dv, u)}{Y^{(n)}(v, u)} \right| du,$$

which tends to zero by Doob's inequality, (5.1), Conditions (C1) and (C3) and the assumptions $n w_n b_n^2 \tilde{b}_n^2 \to \infty$ and $w_n = o(b_n \tilde{b}_n)^2$. Doob's inequality is applicable here since the assumption that $EN_i(1) < \infty$ implies that M_i is a square integrable martingale by Aalen (1978), page 723. □

The following lemma, similar to Lemma 4.2 of Aalen (1976), is useful for the proof of Proposition 1.

LEMMA 1. *Let* $X \sim$ binomial(n, p), $0 < p \le 1$, *and define* $1/X$ *to be* 0 *if* $X = 0$. *Then, for each positive integer* k,

$$E\left(\frac{1}{X}\right)^k \le \left(\frac{k+1}{np}\right)^k.$$

PROOF.

$$\begin{aligned} E\left(\frac{1}{X}\right)^k &= \sum_{i=1}^n \frac{1}{i^k} \frac{n!}{i!(n-i)!} p^i q^{n-i} \\ &= \sum_{i=1}^n \frac{1}{i^k} \frac{(i+1)\cdots(i+k)}{(i+k)!} \frac{n!}{(n-i)!} p^i q^{n-i} \\ &\le \sum_{i=1}^n (k+1)^k \frac{n!}{(i+k)!(n-i)!} p^i q^{n-i} \\ &= \frac{(k+1)^k n!}{p^k (n+k)!} \sum_{i=1}^n \frac{(n+k)!}{(i+k)!(n-i)!} p^{i+k} q^{n-i} \\ &\le \left(\frac{k+1}{np}\right)^k. \end{aligned}$$

□

LEMMA 2 (i.i.d. case). *Suppose that the conditions of Proposition* 1 *hold. Then*

(i) *For each positive integer* k,

$$\sup_{z, s \in \mathcal{T}_z, n} E\left[\frac{n w_n}{Y^{(n)}(s, z)}\right]^k < \infty.$$

(ii) *For each* $z \in [0,1]$

$$\int_{\mathscr{T}_z} P\big(Y^{(n)}(s,z) = 0\big)\, ds \le e^{-mnw_n},$$

where $m > 0$ *is a lower bound for* f *on* supp(α).

(iii) *If* $nw_n \to \infty$, *then for each* $z \in [0,1]$

$$E\int_{\mathscr{T}_z}\left|\frac{nw_n}{Y^{(n)}(s,z)} - g(s,z)\right| ds \to 0.$$

PROOF. If $s \in \mathscr{T}_z$, then $Y^{(n)}(s,z)$ has a binomial distribution with parameters n and $p^{(n)}(s,z) = \int_{\mathscr{I}_z} f(s,u)\,du \ge mw_n$, where m is defined in (ii) above. Hence, by Lemma 1,

$$E\left[\frac{nw_n}{Y^{(n)}(s,z)}\right]^k \le \left(\frac{(k+1)nw_n}{nmw_n}\right)^k,$$

which proves (i). Also, if $s \in \mathscr{T}_z$, then

$$P\big(Y^{(n)}(s,z) = 0\big) \le (1 - mw_n)^n \le e^{-mnw_n},$$

which proves (ii). For $s \in \mathscr{T}_z$, $p^{(n)}(s,z) = O(w_n)$, so that

$$\text{(5.2)} \quad \operatorname{Var}\left(\frac{Y^{(n)}(s,z)}{nw_n}\right) = \frac{np^{(n)}(s,z)\big(1 - p^{(n)}(s,z)\big)}{(nw_n)^2} = O\left(\frac{1}{nw_n}\right) \to 0$$

and, using the continuity of f on supp(α),

$$\text{(5.3)} \qquad E\left(\frac{Y^{(n)}(s,z)}{nw_n}\right) = \frac{1}{w_n}\int_{\mathscr{I}_z} f(s,u)\,du \to f(s,z).$$

Now

$$E\left|\frac{nw_n}{Y^{(n)}(s,z)} - g(s,z)\right| \le E\left|\frac{nw_n}{Y^{(n)}(s,z)} - I\big(Y^{(n)}(s,z) \ne 0\big)g(s,z)\right| + g(s,z)P\big(Y^{(n)}(s,z) = 0\big).$$

The integral over $\mathscr{T}_z$ of the second term here tends to zero by part (ii) of Lemma 2. Note that $g(\cdot, z)$ is bounded on $\mathscr{T}_z$ since f is assumed to be bounded away from zero on supp(α). The first term is bounded above by

$$g(s,z)E\left\{\left|\frac{nw_n}{Y^{(n)}(s,z)}\right|\left|f(s,z) - \frac{Y^{(n)}(s,z)}{nw_n}\right|\right\},$$

which tends to zero by the Cauchy–Schwarz inequality, part (i) of Lemma 2 with $k = 2$, (5.2) and (5.3). The proof of (iii) is completed by applying the dominated convergence theorem to

$$\int_{\mathscr{T}_z} E\left|\frac{nw_n}{Y^{(n)}(s,z)} - I(Y^{(n)}(s,z) \neq 0)g(s,z)\right| ds. \qquad \Box$$

PROOF OF PROPOSITION 1. Condition (A1) follows directly from Lemma 2(iii). Condition (A2) is proved using Lemma 2(ii):

$$E\left[\text{Leb}\{s \in \mathscr{T}_z: Y^{(n)}(s,z) = 0\}\right] = \int_{\mathscr{T}_z} P(Y^{(n)}(s,z) = 0)\, ds$$
$$\leq e^{-mnw_n} = o\left(\frac{1}{\sqrt{nw_n}}\right),$$

where we have used $nw_n \to \infty$. Conditions B, (C1) and (C2) are proved in a similar way, except that parts (ii) and (iii) of Lemma 2 need to be slightly modified. □

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