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A NONPARAMETRIC CALIBRATION ANALYSIS

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In this paper we discuss a new approach to solve calibration problems in a nonparametric setting. This approach is appealing because it yields estimates of the required quantities directly. The method combines kernel and robust estimation techniques. It relies on strong approximations of the estimating process and the extreme value theorem of Bickel and Rosenblatt. Using these results, we first obtain robust pointwise estimates of the parameters of interest. Second, we set up asymptotic simultaneous tolerance regions for many unknown values of the quantity to be calibrated. The technique is illustrated on a radiocarbon dating problem. The nonparametric calibration procedure proves to be of practical, as well as theoretical interest; moreover, it is quick and simple to implement.

1. Introduction. Statistical calibration analyses provide a way to predict a quantity from the observation of another one by using a dose–response type relationship. The problem occurs in industry or the biological sciences when the quantity to be calibrated is hard or expensive to measure, or is not observable. In many situations, the knowledge of the experimental process can hardly be translated into a parametric model for the dose-response relationship. A tempting alternative may be provided by a nonparametric modeling.

Let Z denote the random response variable we observe. The unknown scalar quantity of interest, ξ_0, is related to Z through the regression model

$$Z = r(\xi_0) + e, \tag{1}$$

where e is a centered random variable with finite variance. r is some unknown but smooth function. It is supposed to be strictly monotonic and twice continuously differentiable on the calibration domain $\mathcal{I} = [a, b]$. The additional information about r is given by experimental data obtained from a *calibration experiment*, (X_i, Y_i), $i = 1, \ldots, n$, and following the same regression model

$$Y_i = r(X_i) + \varepsilon_i, \qquad i = 1, \ldots, n. \tag{2}$$

The X_i's are measured with negligible error compared to the Y_i's. The ε_i's are independent random variables with zero mean and finite variances. The training sample $\{(X_i, Y_i),\ i = 1, \ldots, n\}$, is independent of Z.

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The calibration problem is of great practical importance in biology and medicine [Finney (1978); Hubert (1992)]: bioassay data analysis requires calibration techniques to determine the amount of an agent, for instance, a hormone concentration ξ_0, from the measurement of a response Z, which may be a radioactivity count (RIA experiments) or an optical density (ELISA experiments). The conversion of radiocarbon dates to calendar dates is another case of calibration: radiocarbon measures on tree-ring dated wood have demonstrated the need to correct or calibrate radiocarbon dates. Clark (1979, 1980) discussed the statistical aspects of the construction and use of a calibration curve for carbon-14 dates, as well as some of its geophysical and archeological implications. In the nuclear industry, accurate determination of some state variables of processing tanks is required. Knafl, Sacks, Spiegelman and Ylvisaker (1984) provided a calibration procedure to evaluate the volume of the material contained in a tank from the measurement of a differential pressure.

As clearly shown by Osborne (1991) in a thorough review of the area, calibration is usually discussed in a parametric setting and most of the papers deal with a Gaussian linear model. To fill the gap between the traditional linear-model approach and the practical need of more flexible regression functions r, some authors in the 1980s have developed a nonparametric approach: Clark (1980) discussed calibration of radiocarbon dates using a *convolution-smoothing estimator* of r; Knafl, Sacks, Spiegelman and Ylvisaker (1984) proposed new procedures to cope with systematic departures from an exact linear model and an extension of the method to suit smoother regression functions; Müller and Schmitt (1988) introduced kernel estimates of quantal dose–response curves. The nonparametric procedures are designed on the same pattern as that of the classical parametric ones: they follow a two-step estimation process. In the first step, the calibration experiment is used to estimate r and construct confidence intervals about the regression function. The second step solves the calibration problem by inverting prediction intervals for the response variable Z. The two-step structure contributes to increase the computational complexity of nonparametric methods. Moreover, the objective of calibration is not the estimation of a regression function, the latter being possibly thought of as a nuisance parameter. Our main concern is indeed the estimation of the parameter ξ_0 corresponding to observations Z satisfying (1). We therefore propose in this paper an approach leading to a direct statistical inference on the parameter of interest. This approach is appealing for two reasons: First, it introduces some robustification of calibration; second, it yields a convenient construction of simultaneous tolerance intervals for calibration.

The proposed method combines classical nonparametric techniques with robust estimation methods. An estimate $\hat{\xi}$ of ξ_0 is defined as a solution, if it exists, of the estimating equation

$$H_n(\xi, Z) = \frac{1}{n}\sum_{i=1}^{n} \frac{1}{h_n} K\left(\frac{\xi - X_i}{h_n}\right)\Psi(Y_i - Z) = 0 \tag{3}$$

with respect to ξ. K is a density kernel, $\{h_n\}$ is a sequence of bandwidths and Ψ is an odd nondecreasing function. Since (3) may have several solutions, we define the estimate $\hat{\xi}$ to be the solution of (3) that is closest to the value X_i, whose corresponding observation Y_i is the nearest to Z. In practical implementation, we can use the Newton–Raphson method with starting value X_i to find such a solution. We essentially think of two different types of Ψ-functions: Ψ is the identity function or Ψ is a bounded function. The choice of a bounded Ψ, for instance Huber's classical function $\Psi(u) = \max\{-\kappa, \min(u, \kappa)\}$, $\kappa > 0$, is expected to give protection against training data containing outliers, generated by heavy-tailed distributions. This issue is discussed in Section 3. If $\Psi(u) = u$, the solution of (3) is $\hat{\xi} = \hat{r}^{-1}(Z)$, where $\hat{r}$ is the usual Nadaraya–Watson kernel estimate of r [Nadaraya (1964) and Watson (1964)]. That is, $\hat{\xi}$ is the classical calibration estimate. However, in a nonparametric context, techniques for constructing interval estimates to accompany this estimate have not been much developed. Our aim is to provide a new answer to this question.

If a single unknown ξ_0 is to be predicted based on Z satisfying (1), a natural way to compute a confidence interval for ξ_0 is to consider the set $\{\xi, |H_n(\xi, Z)| \le c\}$, where the bound c is to be determined later. This is an extension of calibrating against a least squares line by considering the residual $Z - \hat{r}(\xi)$. Difficulties arise when, as in many calibration situations, a single calibration experiment is performed and used repeatedly to provide many estimations of $\xi_1, \xi_2, \ldots,$ corresponding to new observations of the response variable $Z_1, Z_2, \ldots$. This uncertainty approach was originated by Scheffé (1973) and discussed by Lechner, Reeve and Spiegelman (1982) and Mee, Eberhardt and Reeve (1991) in the framework of a linear model. In a nonparametric setting, Clark (1979) solved the multiple-use case by using Bonferroni inequalities and obtained somewhat conservative confidence regions. Knafl, Sacks, Spiegelman and Ylvisaker (1984) proposed new techniques to extend Scheffé's method to nonparametric estimates of r. The main step of their procedure is the construction of a confidence band for r, suitably expanded to account for the variability of observations of the response variable Z. To construct an appropriate confidence band, Knafl, Sacks, Spiegelman and Ylvisaker used numerical differentiation techniques. As a result, their procedure is cumbersome to use because it requires the evaluation of multidimensional integrals. In response to this difficulty, Carrol, Spiegelman and Sacks (1988) proposed a simpler numerical solution but modified the uncertainty statement on which the intervals were based. In this paper, we give another solution to the multiple-use problem. The resulting calibration intervals are simpler to compute than those obtained using the procedure of Knafl, Sacks, Spiegelman and Ylvisaker yet have the same probability interpretation.

The main results of this paper are derived from the asymptotic properties of H_n and the study of the limiting distribution of its maximal deviation. Therefore we give in the next section some technical lemmas. The strong consistency and the asymptotic normality of the rescaled estimate $\hat{\xi}$ are

established in Section 3. Robustness properties are also investigated through a simulated example. In Section 4, the multiple-use calibration procedure based on H_n is discussed. For an illustrative purpose, it is applied on a data set from Clark (1975) for tree-ring calibration of radiocarbon dates. Finally, closing comments are made in Section 5.

2. Preliminary results.

2.1. *Regularity conditions.* We assume that $(X_1, Y_1), \ldots, (X_n, Y_n)$ is a random sample drawn from the distribution P of a two-dimensional random vector (X, Y) such that $Y = r(X) + \varepsilon$. Let F be the distribution function of (X, Y). G denotes the marginal d.f. of X and $F_{Y|X}$ the conditional d.f. of Y given X. Let $f(x, y)$ and $g(x)$ be the joint density and marginal density of (X, Y) and X, respectively. P_n denotes the empirical distribution, $P_n = n^{-1}\sum_{i=1}^{n}\delta_{(X_i, Y_i)}$ and $Z_n = n^{1/2}(P_n - P)$ is the empirical process of $(X_1, Y_1), \ldots, (X_n, Y_n)$.

Given a specified value z_c of the response variable Z that is related to ξ_0 through (1), a point estimate of $\xi_c = r^{-1}(z_c)$ is defined as a zero in ξ of

$$H_n(\xi, z_c) = \int K_{h_n}(\xi - x)\Psi(y - z_c)\, dP_n(x, y)$$

with $K_{h_n}(u) = h_n^{-1}K(h_n^{-1}u)$.

We first give the regularity conditions; each result may require only part of them to be derived.

(A1) (a) Ψ is odd, nondecreasing and piecewise twice continuously differentiable with bounded derivatives.

(b) r is monotone and twice continuously differentiable on a bounded interval of calibration $J = [a, b]$.

(A2) (a) K is symmetric, twice continuously differentiable and has a compact support $[-A, A]$, $K(A) = K(-A) = 0$, $\int K(u)\, du = 1$.

(b) $\int |u \log|u||^{1/2}|K'(u)|\, du < \infty$.

(c) K''' exists and $\int |u \log|u||^{1/2}|K''(u)|\, du < \infty$.

(A3) (a) The conditional densities $f(y|x)$ are symmetric for all x and they have bounded partial derivatives $(\partial/\partial x)f(y|x)$ and $(\partial^2/\partial x^2)f(y|x)$, uniformly in $x \in J$. $\Psi(\cdot)(\partial^2/\partial x^2)f(\cdot|x) \in L^1(\mathbb{R})$, for $x \in J$.

(b) g is twice differentiable on an open interval containing J; its second derivative is bounded, $\inf_J g(x) > 0$.

(c) $\sup_x \int f(x, y)\, dy < \infty$.

(A4) Define $T\colon \mathbb{R}^2 \to [0, 1]^2$ by $T(x, y) = (G(x), F_{Y|X}(y|x))$.

(a) The inverse transformation T^{-1} exists and is measurable.

(b) Let $\phi_{h,\xi}(x, y) = K_h(\xi - x)\Psi(y - z_c)$. $\phi_{h,\xi} \circ T^{-1}$ is twice continuously differentiable.

(A5) $\inf_{\xi \in \mathscr{J}} E(\Psi'(Y - r(\xi))|X = \xi) > \tau_0 > 0$.

(A6) Let $v(\xi) = E(\Psi^2(Y - r(\xi))|X = \xi)g(\xi)$. v is differentiable with a bounded derivative, $\sup_{\xi \in J} v(\xi) < \infty$ and $\inf_{\xi \in J} v(\xi) > v_0 > 0$.

There exists an increasing sequence α_n of positive numbers satisfying $\alpha_n \to \infty$ as $n \to \infty$ and $\sum \alpha_n^2 < \infty$, such that:

(M) (a) $E(\Psi^2(Y)) < \infty$ and $\sup_x \int \Psi^2(y)f(x, y)\,dy < \infty$.
(b) $\sup_{\xi \in J} \sup_x \int_{|y| > \alpha_n} \Psi^2(y - r(\xi))f(x, y)\,dy \le O(h^2)$.

(M′) Ψ is bounded.

(a) $\sup_x \int_{|y| > \alpha_n} f(x, y)\,dy \to 0$ when $n \to \infty$.
(b) $\sup_x \int_{|y| > \alpha_n} f(x, y)\,dy \le O(h^2)$.

Assumptions (A1) and (A3) asking for oddness and monotony of Ψ and symmetry of the conditional densities are common assumptions in robust regression. They are sufficient to ensure the consistency of the estimates. Condition (A2) specifies the class of kernels K. Assuming (A4) is necessary to apply the bivariate invariance principle of Tusnady (1977) and to approximate H_n by a Gaussian process. Note that (A5) is trivially fulfilled for $\Psi(u) = u$.

The moment conditions (M) and (M′) ensure the vanishing of some remainder terms. (M) will be used for unbounded Ψ only, while (M′) will be used in the case of bounded Ψ. The following lemmas and propositions will be stated for unbounded Ψ functions, the equivalent statements on bounded Ψ function being obtained by replacing assumption (M) with (M′). Let us also notice that the conditions (b) in (M) and (M′) are refinements of conditions (a) that will be used to study the statistic $H_n(\xi, r(\xi))$.

Unless otherwise stated, the integration domain is the entire real line. As a minimal assumption, the bandwidth is assumed to vary with n according to the classical conditions, $h_n \to 0$ and $nh_n \to \infty$, which will be refined throughout the discussion. All limits have to be thought of as limits when n tends to infinity. To simplify the notation, we will generally write h instead of h_n.

2.2. *Gaussian approximation of H_n.* We consider the statistic of interest $\{(H_n - E(H_n))(\xi, z_c),\ \xi \in [a, b]\}$, for each fixed z_c, as a continuous stochastic process on $[a, b]$ and approximate it by an appropriate stationary Gaussian process. More precisely, we have the decomposition

$$(H_n - E(H_n))(\xi, z) = n^{-1/2}\rho_n(\xi) + \eta_n(\xi), \tag{4}$$

where

$$\rho_n(\xi) = \int\int_{|y| \le \alpha_n} K_h(\xi - x)\Psi(y - z_c)\,dB^F(x, y) \tag{5}$$

and η_n is an error term we will consider subsequently. B^F denotes the Brownian bridge based on the measure with distribution function F, so that for $s, s', t, t' \in \mathbb{R}^2$,

$$E\big(B^F(s,t)B^F(s',t')\big) = F(s \wedge s', t \wedge t') - F(s,t)F(s',t').$$

α_n is the sequence of positive numbers introduced in assumptions (M) and (M′).

The asymptotic behavior of the leading term is given in the next lemma. The proof of this result is adapted from Silverman (1976) and Mack and Silverman (1982), and is detailed in Gruet (1992).

LEMMA 1. *Under the assumptions* (A2) *and* (M)(a),

$$\text{if} \quad \frac{\big(\log h_n^{-1}\big)^{1/2}}{(nh_n)^{1/2}} \to 0, \quad \text{then} \quad n^{-1/2} \sup_{\xi \in \mathscr{I}} |\rho_n(\xi)| = o(1) \quad a.s.$$

We now consider the error term η_n. η_n splits up into two terms:

$$(6) \quad \varepsilon_n(\xi) = n^{-1/2} \int\int_{|y| \le \alpha_n} K_h(\xi - x)\Psi(y - z_c)\big[dZ_n(x,y) - dB^F(x,y)\big]$$

and

$$(7) \quad t_n(\xi) = \int\int_{|y| > \alpha_n} K_h(\xi - x)\Psi(y - z_c)d(P_n - P)(x,y).$$

ε_n is the error of approximation made in replacing the empirical process by a Brownian bridge. t_n is a truncation error term. Each term is now being considered.

Truncation error term. Note that this term does not appear if Y is almost surely bounded. Otherwise,

$$\begin{aligned} |t_n(\xi)| &\le \int\int |K_n(x - \xi)||\Psi(y - z_c)|1_{|y| > \alpha_n} d(P_n + P)(x,y) \\ &= t_1(\xi) + t_2(\xi). \end{aligned}$$

By the Borel–Cantelli lemma, $\sup_\xi t_1(\xi)$ is zero with probability 1. If Ψ is not bounded, the expectation term $\sup_\xi |t_2(\xi)| = o(1)$ with (A2) and (M)(a), since Ψ is monotone and $\{\alpha_n\}$ increase to ∞. The same result is true if Ψ is bounded if we assume (M′)(a). This yields the uniform almost sure convergence to 0 of the truncation error term t_n.

Approximation error term. The evaluation of the approximation error term ε_n rests on a strong uniform approximation of the bivariate empirical process, based on independent random variables uniformly distributed over $[0,1]^2$, by a bivariate Brownian bridge [Tusnady (1977)]. To apply this result, we transform our data with the help of the transformation T: $\mathbb{R}^2 \to [0,1]^2$ [Rosenblatt (1952)] defined as $T(x,y) = (G(x), F_{Y|X}(y|x))$. Let μ_n denote the empirical measure of the transformed sample $(U_i, V_i) = T((X_i, Y_i))$, $i =$

$1, \dots, n$, and $\tilde{Z}_n$ there empirical process. Under assumption (A4)(a), we have $P_n(\mathscr{A}) = \mu_n(T(\mathscr{A}))$ for any Borel set $\mathscr{A}$ of $\mathbb{R}^2$. By classical arguments and (A4)(b), the last equality can be extended to the class of continuous bounded functions. With an integration by parts, we can write

$$\sup_{\xi \in \mathscr{I}} |\varepsilon_n(\xi)| \le n^{-1/2} \sup_{[0,1]^2} |\tilde{Z}_n(x, y) - B(x, y)| h^{-1} \int |K'(u)|\, du \times \left\{ \int_{-\alpha_n}^{\alpha_n} \Psi'(y - z_c)\, dy + |\Psi(\alpha_n - z_c)| + |\Psi(-\alpha_n - z_c)| \right\}.$$

From this formula, ε_n can be evaluated with the help of the invariance principle of Tusnady: for each n, we can find a suitable probability space supporting both $\hat{Z}_n$ and a version of the Brownian bridge based on the uniform measure on $[0, 1]^2$, B, such that

$$\sup_{x, y} |\tilde{Z}_n(x, y) - B(x, y)| = O\left(n^{-1/2} (\log n)^2\right)$$

with probability 1. Thus, $\sup_{\xi \in \mathscr{I}} |\varepsilon_n(\xi)| \le C(\log n)^2 / nh |\Psi(\alpha_n)|$ a.s. with some constant $C < \infty$.

This yields the following lemma:

LEMMA 2. *Suppose assumptions* (A1)–(A4) *and* (M)(a) *hold. Then*

$$\sup_{\xi \in \mathscr{I}} \left| (H_n - E(H_n))(\xi, z_c) - n^{-1/2} \rho_n(\xi) \right| = O\left(\frac{(\log n)^2}{nh_n} |\Psi(\alpha_n)| \right) + o(1) \quad a.s.,$$

where ρ_n *is defined by* (5).

2.3. *Asymptotic maximal deviation of* H_n. Up to now we have considered the statistic $H_n(\xi, Z)$ conditionally on a specified or fixed value of the response variable Z. The third lemma of this section deals with the statistic $H_n(\xi) = H_n(\xi, r(\xi))$ and gives the limiting distribution of the maximum absolute value of the normalized statistic $D_n(\xi) = (nh)^{1/2} v^{-1/2}(\xi)(H_n - E(H_n))(\xi)$, where $v(\xi) = E(\Psi^2(Y - r(\xi)) | X = \xi) g(\xi)$.

LEMMA 3. *Let* $h = n^{-\beta}$, $0 < \beta < 1/2$, *and suppose* (A1)–(A6) *and* (M) *hold. If* $(nh)^{-1/2} |\Psi(\alpha_n)| \to 0$ *when* $n \to \infty$, *then*

$$P\left\{ (2 \log h^{-1})^{1/2} \left(\sup_{\xi \in J} \left| (nh)^{1/2} (\lambda v(\xi))^{-1/2} (H_n - E(H_n))(\xi) \right| - d_h \right) < z \right\} \to \exp(-2 \exp(-z)), \quad \text{when } n \to \infty,$$

with $\lambda = \int K^2(u)\, du$, $d_h = (2 \log h^{-1})^{1/2} + (2 \log h^{-1})^{-1/2} \log((2^{1/2}\pi)^{-1} C_2^{1/2})$ *and* $C_2 = (2\lambda)^{-1} \int (K'(u))^2\, du$.

PROOF. We first use the Gaussian approximation formula (4):

$$D_n(\xi) = h^{1/2} v_n^{-1/2}(\xi)\rho_n(\xi) + h^{1/2}\left(v^{-1/2} - v_n^{-1/2}\right)(\xi)\rho_n(\xi) + (nh)^{1/2} v^{-1/2}(\xi)\varepsilon_n(\xi) + (nh)^{1/2} v^{-1}(\xi)(t_n)(\xi), \tag{8}$$

where $v_n(\xi) = \int_{|y| \le \alpha_n} \Psi^2(y - r(\xi)) f(\xi, y)\, dy$. ρ_n, t_n and ε_n are adapted to the process of present interest $H_n(\xi, r(\xi))$ by replacing z_c with $r(\xi)$ in the formulas (5)–(7). For instance,

$$\rho_n(\xi) = \int\int_{|y| \le \alpha_n} K_h(x - \xi)\Psi(y - r(\xi))\, dB^F(x, y).$$

Clearly, the results of Lemmas 1 and 2 can be extended to these modified processes. It is shown in the Appendix that the three last terms on the r.h.s. of (8) are negligible, uniformly in ξ.

Hence $D_n(\xi) = \rho_{n,1}(\xi) + o_P(1)$, where $\rho_{n,1}(\xi) = h^{1/2} v_n^{-1/2}(\xi)\rho_n(\xi)$. Using arguments analogous to those used in Bickel and Rosenblatt (1973), Liero (1982) or Härdle (1989), $\rho_{n,1}$ can be successively approximated by normalized Gaussian process sharing the same covariance structure and thus having the same limit distribution. The final approximating process is the stationary Gaussian process $Y_h(t) = h^{-1/2}\int K(h^{-1}(t - u))\, dW_0(u)$, where $\{W_0(t),\ t \in (-\infty, \infty)\}$ is a standard Wiener process. Y_h was studied by Bickel and Rosenblatt (1973), who proved that the limiting distribution of its maximal absolute deviation is the Gumbel distribution. We can then apply the result of Bickel and Rosenblatt to D_n:

$$\begin{aligned}
&\lim_{n\to\infty} \mathrm{P}\left\{\left(2\log h^{-1}\right)^{1/2}\left(\sup_{0 \le t \le h^{-1}} |\lambda^{-1} D_n(t)| - d_h\right) < z\right\} \\
&\quad = \lim_{n\to\infty} \mathrm{P}\left\{\left(2\log h^{-1}\right)^{1/2}\left(\sup_{0 \le t \le h^{-1}} |\lambda^{-1} Y_h(t)| - d_h\right) < z\right\} \\
&\quad = \exp(-2\exp(-z)).
\end{aligned}$$

□

3. Robust nonparametric calibration. We now turn to the study of the calibration method defined by the estimating equation (3). Recall that $\hat{\xi}$ is defined as a solution of $H_n(\xi, Z) = 0$. Given a specified value of the response variable $\{Z = z_c\}$, we first show that $\hat{\xi}$ is a consistent estimate of $\xi_c = r^{-1}(z_c)$. The parameter of interest ξ_0, defined in (1) and denoted by ξ_c when we work conditional on Z, is assumed to belong to the calibration domain $\mathcal{I} = [a, b]$.

3.1. *Consistency.*

PROPOSITION 1. *Suppose assumptions* (A1)–(A4) *and* (M) *hold. Then* $\hat{\xi}$ *converges to* ξ_c *almost surely if*

$$h_n \to 0 \quad \textit{and} \quad \frac{(\log n)^2}{nh_n}|\Psi(\alpha_n)| \to 0 \quad \textit{when } n \to \infty.$$

REMARK. If we choose $\Psi(x) = x$, $\alpha_n = n^{1/2}(\log n)^{1/2+\eta}$ and $h = n^{-\beta}$, with $\eta, \beta > 0$, the condition for strong consistency is $0 < \beta < 1/2$. Moreover, if Y is bounded a.s. or if Ψ is bounded, then the condition becomes $0 < \beta < 1$, which is the weakest possible condition to be imposed on h in order to obtain asymptotic consistency.

PROOF. Under the assumptions (A1)–(A3) and the moment condition (M), it follows from the weak law of large numbers that $H_n(\xi, z_c)$ converges in probability to a limit function $H(\xi)$ for all ξ, with

$$H(\xi) = E\big[\Psi(Y - z_c)|x = \xi\big]g(\xi).$$

Since Ψ is odd, the conditional densities $f(y|x)$ are symmetric and r is one-to-one, $H(\xi)$ has a unique zero at ξ_c. If we prove the uniform almost sure convergence of H_n to H over $\mathscr{I}$, then we can deduce almost surely that $H(\hat{\xi}) \to 0$ from $|H_n(\hat{\xi}, z_c) - H(\hat{\xi})| \to 0$ a.s. and $H_n(\hat{\xi}, z_c) = 0$. As a result, we obtain the consistency of $\hat{\xi}$.

The uniform almost sure convergence of H_n to H over $\mathscr{I}$ is derived from Section 2:

(i) By standard arguments, $\sup_{\xi \in J}|E(H_n(\xi)) - H(\xi)| = O(h^2)$, using assumptions (A3) and (M)(a).

(ii) The convergence of the random term $\sup_{\xi \in \mathscr{I}}|(H_n - E(H_n))(\xi, z_c)|$ to 0 is a direct consequence of Lemmas 1 and 2. □

3.2. *Asymptotic normality.*

PROPOSITION 2. *Let* (A1)–(A5) *and* (M) *be satisfied. If*

$$(nh^3)^{-1}(\log n)^2|\Psi(\alpha_n)| \to 0$$

when $n \to \infty$, *then*

$$(nh)^{1/2}\big(\lambda v(\xi_c)\big)^{-1/2}\tau(\xi_c)\big(\hat{\xi} - \xi_c - d_K(\xi_c)h^2\big) \to_{\mathscr{D}} \mathscr{N}(0,1),$$

where $\tau(\xi) = E(\Psi'(Y - r(\xi))|X = \xi)r'(\xi)g(\xi)$ *and* $d_K(\xi)$ *is uniformly bounded on* $\mathscr{I}$.

PROOF. The proof follows from a Taylor series expansion of $H_n(\xi, r(\xi))$ around $\hat{\xi}$, noting that, under the regularity conditions (A1)–(A3) and (M),

$$H_n'(\xi_c) = n^{-1}\sum_{i=1}^{n} h^{-2}K'\big(h^{-1}(\xi_c - X_i)\big)\Psi(Y_i - z_c)$$

tends to $\tau(\xi_c)$ in probability if $h \to 0$ and $nh^3 \to \infty$; condition (A5) ensures that $|\tau(\xi_c)| > 0$. $d_K(\xi_c)$ is easily obtained from a classical bias calculation. The only technical point is to show that the remainder term $R_n = (nh)^{1/2}(\hat{\xi} - \xi_c)(H_n'(\xi^*) - H_n'(\xi_c))$, where $|\xi^* - \xi_c| \le |\hat{\xi} - \xi_c|$ and ξ^* is random, tends to 0 in probability. However, the results of the previous section about H_n can be easily extended to its derivative H_n', using (A2)(c) and the conditions (b) of

(M) or (M′). Thus we can write $\sup_{\mathscr{F}}|(H_n' - E(H_n'))(\xi)| \le O(((\log n)(nh)^{-3})^{1/2})$ almost surely, if $(nh^3)^{-1}(\log n)^2|\Psi(\alpha_n)| \to 0$. It follows that $|R_n| \le c(nh)^{1/2} \times|H(\hat{\xi}) - H_n(\hat{\xi}, z_c)|\sup_{\mathscr{F}}|(H_n' - E(H_n'))(\xi)| \le O_P((nh^3)^{-1/2} \log n)$, where $c > 0$ is a constant. Hence Proposition 2. □

Application. In calibration applications, since we are interested in confidence intervals for ξ_0, whose corresponding observation Z is a random variable, it is more natural to compute confidence sets directly based on H_n. For instance, if we assume that Z is Gaussian with variance σ^2 and if we ignore the bias term (which amounts to assuming $h = n^{-\beta}$, $\beta > 1/5$ or using a higher order kernel), then

$$\left\{\xi, |H_n(\xi, Z)| \le \Phi^{-1}\left(1 - \frac{\alpha}{2}\right)\left(\sigma^2 + \frac{\lambda\hat{v}_n}{nh}\right)^{1/2}\right\}$$

is a calibration set for ξ_0 with asymptotic confidence level $1 - \alpha$. Φ is the Gaussian distribution function. $\hat{v}_n$ is a consistent estimate of $v(\xi_0)$, for instance,

$$\hat{v}_n = \frac{1}{nh}\sum_{i=1}^{n} K_h\left(X_i - \hat{\xi}\right)\Psi^2(Y_i - Z).$$

If we are interested in confidence intervals for ξ_c, which corresponds to a fixed, predetermined value of the response z_c, we can compute a confidence set with asymptotic level $1 - \alpha$ as $\{\xi, |H_n(\xi, z_c)| \le \Phi^{-1}(1 - \alpha/2)(\hat{v}_n\lambda/nh)^{1/2}\}$.

3.3. *Minimax robustness*. Following Härdle and Gasser (1984), who investigated robustness properties of M-type smoothers, we may ask ourselves whether incorporating robust estimation methods in the estimating equation (3) will result in some robustification of the calibration estimate $\hat{\xi}$. As a matter of fact, we can show that the estimate derived from (3) is robust against symmetric departures from a symmetric model distribution.

In analogy with Huber's theory of robust estimation, we define the most robust estimate $\hat{\xi}$ as the solution to the minimax variance problem: Find the function Ψ that minimizes the maximum asymptotic variance of $\hat{\xi}$ given by Proposition 2,

$$V_\xi(\Psi, f) = \frac{\lambda v(\xi)}{\tau^2(\xi)} = \frac{\lambda}{r'(\xi)g(\xi)}\frac{E\left(\Psi^2(Y - r(\xi)) \mid X = \xi\right)}{\left\{E\left(\Psi'(Y - r(\xi)) \mid X = \xi\right)\right\}^2},$$

when the underlying density function $f(y|x)$ varies over the usual contamination model $\mathscr{F} = \{f(y|x) = (1 - \eta(x))\tilde{f}(y - r(x)) + \eta(x)l(y - r(x))\}$, where $\tilde{f}$ is a fixed density function, $0 < \eta(x) < 1$, l is any symmetric density function and $-\log(\tilde{f}(\cdot - r(x)))$ is convex. From Huber (1964) and Härdle and

Gasser (1984) we know that this problem admits a solution, that is, there is an f_0 and a Ψ_0 such that

$$\sup_{\mathscr{F}} V_\xi(\Psi_0, f) = V_\xi(\Psi_0, f_0) = \inf_{\Psi} V_\xi(\Psi, f_0).$$

As a consequence, $\hat{\xi}$ computed with the optimal Ψ_0 is minimal when the conditional density function varies in the contamination neighborhood $\mathscr{F}$. Table 1 in Härdle and Gasser (1984) gives some evidence that the use of Huber's classical function $\Psi_\kappa(u) = \max\{-\kappa, \min(u, \kappa)\}$, $\kappa > 0$, which is minimax over contamination neighborhoods of the Gaussian distribution, will result in a significant gain in asymptotic efficiency. Practically speaking, it is expected that $\hat{\xi}$ computed with Ψ_κ is less sensitive to outliers in the training data than the classical nonparametric estimate.

In a small simulation study, we compared the performances of the calibration method using $\Psi(u) = u$, which yields the classical nonparametric estimate ξ^*, and $\Psi(u) = \Psi_\kappa(u)$, which yields the more robust estimate $\hat{\xi}$. We chose $r(x) = x^2$ and generated 400 training data sets $\{(X_i, Y_i)\}$ of length $n = 100$: the X_i's were drawn from the uniform distribution on $[0, 1]$; the Y_i's are according to (2) with the residual's density function

$$f(y|x) = \frac{95}{100}\phi(y - r(x)) + \frac{5}{900}\phi\left(\frac{y - r(x)}{9}\right).$$

ϕ denotes the density function of a centered normal variable with variance 0.025^2. The bandwidth was subjectively set to $h = 0.1$ and the cutoff point of Huber's Ψ-function was set to $\kappa = 0.2$. For each simulated data set $\{(X_i, Y_i)\}$, we computed ξ^* and $\hat{\xi}$ corresponding to the specified value of the response variable $z_c = 0.4$, together with the associated confidence intervals of asymptotic level 95% (according to Section 3.2). One simulated data set and the confidence intervals based on this data set are displayed in Figure 1. The average length of the confidence intervals with $\Psi(u) = u$, based on the 400 simulations, is 0.054 and that of the confidence intervals obtained with $\Psi(u) = \Psi_\kappa(u)$ is 0.046, whereas the empirical coverage probabilities are nearly the same (90% and 89.75%, respectively). These results show that using the robust method significantly decreases the length of the intervals (15% on average). On this example, calibrating with $\Psi(u) = u$ leads to longer confidence intervals, which reflects the expected sensitivity to outliers of the estimate ξ^*.

4. A multiple-use calibration procedure. We deal here with the problem of estimating, not a single parameter ξ_0, but different unknown values ξ_j, $j = 1, 2, \ldots$, corresponding to new measurements of the response variable Z,

$$Z_j = r(\xi_j) + e_j, \qquad j = 1, 2, \ldots,$$

with identically distributed centered errors e_j with finite variance σ. In this section, we assume that the distribution of e_j is symmetric and that this

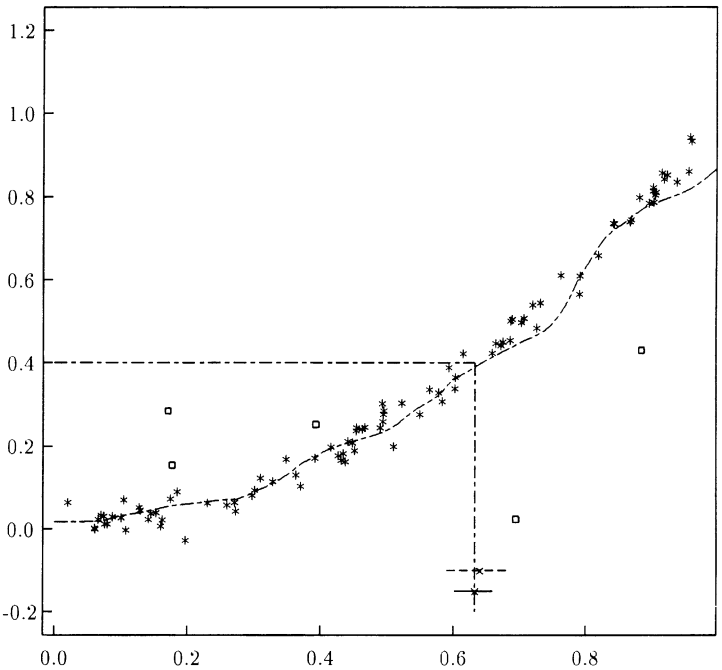

FIG. 1. *The robust calibration method compared with the standard method on a simulated data set. The random variables generated with probability* $5/100$ *from the long-tailed distribution are marked as squares, whereas the normal random variables are marked as asterisks. The confidence interval obtained with* $\Psi(u) = u$ *is shown as a dotted line and the interval obtained with Huber's* Ψ*-function is shown as a solid line.*

distribution function χ has the form

$$\chi(x) = \chi_0\left(\frac{x}{\sigma}\right),$$

where χ_0 is a fixed distribution function.

The problem is now to find calibration intervals for $\xi_1, \xi_2, \ldots,$ on the basis of a single data set $\{(X_i, Y_i),\ i = 1, \ldots, n\}$ obtained from the calibration experiment. In bioassay, for instance, a *standard curve* is performed on which all future assays are to be run. In this situation, one would like to evaluate the conditional probability, given the training sample used to construct the calibration interval, that the interval covers the true value of ξ_j. Therefore, the purpose of this section is to find tolerance sets $\mathscr{C}(Z_j)$, $j = 1, 2, \ldots,$ for ξ_j, $j = 1, 2, \ldots,$ satisfying the asymptotic uncertainty statement

$$\liminf_{n\to\infty} \mathrm{P}\left[\mathrm{P}\left(\xi_j \in \mathscr{C}(Z_j) | \mathscr{E}\right) \geq 1 - \alpha,\ j = 1, 2, \ldots\right] \geq 1 - \delta \tag{9}$$

for given (α, δ). $\mathscr{E} = \{(X_i, Y_i),\ i = 1, \ldots, n\}$ is the outcome of the calibration experiment. This approach enables us to distinguish more drastically the

variability of the calibration experiment outcome $\mathscr{E}$ from that of the measurement outcome Z_j. Moreover, it guarantees the same precision over the entire calibration domain $\mathscr{I}$. Throughout the section, it is assume that $\Psi(x) = x$.

4.1. *Simultaneous tolerance sets*. Since Scheffé (1973), multiple-use calibration procedures have been based on the construction of lower and upper bounds $L(t)$ and $U(t)$ for the calibration curve $r(t)$ such that

$$\mathrm{P}(L(t) \le r(t) \le U(t), t \in \mathscr{I}) \ge 1 - \delta.$$

The bounds L and U usually have the prescribed form

$$U(t) = \hat{r}(t) + c_1(\alpha, \delta)\hat{\sigma} + c_2(\alpha, \delta)S(t),$$
$$L(t) = \hat{r}(t) - c_1(\alpha, \delta)\hat{\sigma} - c_2(\alpha, \delta)S(t),$$

where $\hat{\sigma}$ is an estimate of the variance of the Z_j and $S(t)$ is the standard deviation of $\hat{r}(t)$. Then

$$\mathscr{C}(Z_j) = \left[U^{-1}(Z_j), L^{-1}(Z_j)\right]$$

is the desired calibration interval for ξ_j. The difficulty of the procedure lies in the choice of the factors c_1 and c_2, which are determined to satisfy statement (9).

In their nonparametric calibration approach, Knafl, Sacks, Spiegelman and Ylvisaker (1984) proposed an exact method to compute c_1 and c_2. It rests on the assumption that the observations are Gaussian. The calculation involves integrals of known density functions. However, long and complicated numerical procedures are needed to evaluate the multidimensional integrals and solve related equations. Furthermore, the method is based on the estimation of $\mathrm{P}(\sup_{\mathscr{I}}|Z(t)| \le \alpha)$, where $Z(t) = (S(t))^{-1}(\hat{r}(t) - r(t))$ is a Gaussian process: this is done by computing $\mathrm{P}(\sup_G|Z(t)| \le \alpha)$, where G is a grid of points covering the range of calibration, and interpolating the lower and upper bounds L and U from the grid G to $\mathscr{I}$.

Our derivation of simultaneous calibration intervals is different from that of Knafl, Sacks, Spiegelman and Ylvisaker in two ways: First, we use an asymptotic approach, valid for a wide class of distribution functions of the observations. Our method rests on the asymptotic estimation of $\mathrm{P}(\sup_{\mathscr{I}}|D_n(\xi)| \le a)$ given in Lemma 3. Second, our method is not based on an a priori form of the confidence band for r: for a given $c > 0$, we define calibration sets $\mathscr{C}(Z_j)$ for ξ_j, $j = 1, 2, \ldots,$ by

$$\mathscr{C}(Z_j) = \left\{ \xi \in J, \frac{|H_n(\xi, Z_j)|}{g_n(\xi)} \le c \right\}$$

with $g_n(\xi) = \sum_1^n K_h(\xi - X_i)/n$. The problem is to determine $c = c(\alpha, \delta)$ in order to satisfy the simultaneous probability statement (9). The answer is given by the following proposition.

PROPOSITION 3. *Suppose that* (A1)–(A6) *and* (M) *hold and that the training data follow an homoscedastic error model. If the density function g of the* X_i*'s is constant on the range* $\mathscr{I}' \subset \mathscr{I}$ *of future calibrations, then a value of c which guarantees statement* (9) *is given by*

$$c = \sigma\chi_0^{-1}\left(1 - \frac{\alpha}{2}\right) + s\frac{1}{\sqrt{nh}}\frac{\lambda^{1/2}}{g_0^{1/2}}\left(\frac{q(1-\delta)}{(2\log h^{-1})^{1/2}} + d_h\right),$$

where $\sigma^2 = \mathrm{Var}(e)$, $s^2 = \mathrm{Var}(\varepsilon)$ *and* $g(\xi) \equiv g_0$, $\forall \xi \in \mathscr{I}'$. $q(u) = \log 2 - \log|\log u|$, $h = n^{-\beta}$, $1/5 < \beta < 1/2$ *and* λ, d_h *are as in Lemma* 3.

The proof is given in the Appendix.

4.2. *An illustrative example*. We now illustrate the multiple-use procedure applied to a radiocarbon dating problem. The data set comes from Clark [(1975), Tables 2 and 3]. The calibration experiment consists of 192 replicate radiocarbon measurements on 83 tree-ring dated samples of wood. All dates are measured in years before present and rescaled to lie on $[0, 1]$ for the analysis. From inspection of the histogram of the tree-ring dates (see Figure 2), we propose $g(x) = \gamma I_{\{0 \le x \le 0.1\}} + (\gamma/10) I_{\{0.1 \le x \le 1\}}$ with $\gamma^{-1} = 0.19$ as density function for the X_i. A Kolmogorov test does not reject this hypothesis.

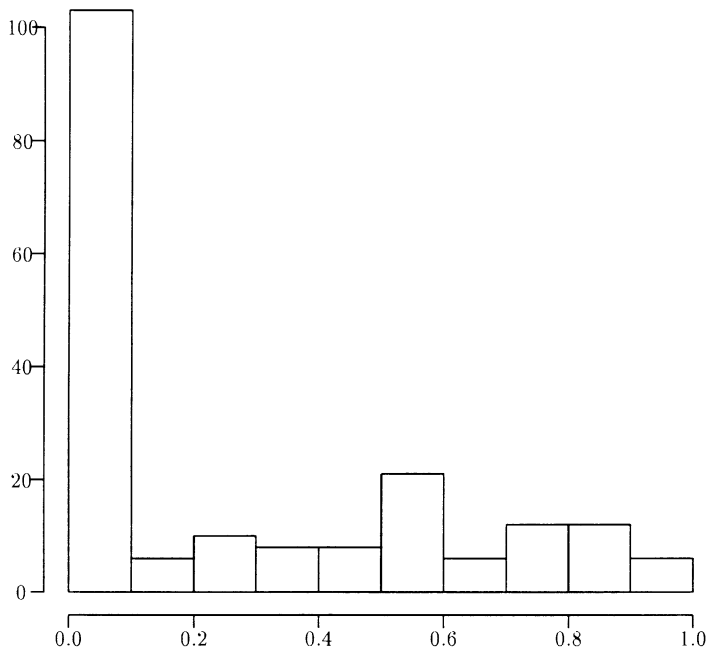

FIG. 2. *Histogram of the tree-ring dates rescaled to lie on* $[0, 1]$.

Calculation of c, the cutoff value, depends on the choice of K, h and the estimates of the variances that are used. We assume $\sigma = s$ and use the Hall, Kay and Titterington (1990) estimate

$$\hat{\sigma}^2 = \frac{1}{n-2} \sum_{i=1}^{n-2} \left(\frac{\sqrt{5}+1}{4} Y_i - \frac{1}{2} Y_{i+1} - \frac{\sqrt{5}-1}{4} Y_{i+2} \right)^2.$$

This estimate is $\sqrt{n}$-consistent and does not alter the conclusion of Proposition 3. Our choice for K is the Epanechnikov kernel $K(u) = \frac{3}{4}(1-u^2)$ if $|u| \leq 1$, and 0 elsewhere. The bandwidth is subjectively set to 0.08 (500 years). The errors e_j are suppose to be Gaussian. The simultaneous calibration intervals are displayed in Figure 3 for selected radiocarbon dates ranging from 600 to 5000 by steps of 50. On this range, the X_i are assumed to be uniformly distributed. Considering a restricted range also allows us to avoid edge effects. The entire calculation used 3 minutes on a Sun 630MP computer.

Although several problems of real practical importance have not been considered here, the fact that a crude application of the proposed procedure gives quite reasonable numerical results is encouraging. Our tolerance inter-

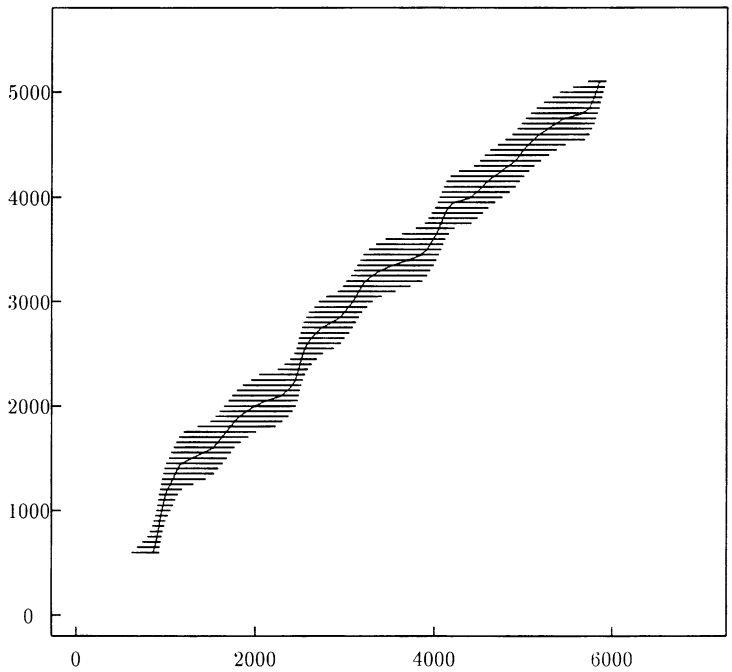

FIG. 3. *Simultaneous tolerance intervals for calibration of radiocarbon dates. Calendar dates are on the x-axis and radiocarbon dates are on the y-axis. Dates are measured in years before present. The solid line connects the estimates of the calendar dates corresponding to the selected radiocarbon dates.*

vals are somewhat longer than the pointwise confidence intervals reported by Clark, but this may indicate the cost of having guaranteed that at least $1 - \delta$ of the intervals will have a conditional probability of at least $1 - \alpha$ of containing the true ξ_j.

5. Discussion. In this paper we have developed a tolerance interval methodology for calibration. The multiple-use procedure has the advantage of being quick and simple to compute: calculation of one factor c directly yields the desired calibration sets. Our procedure is centered around the process H_n and the Bickel and Rosenblatt approximation for the distribution of its maximum deviation. Consequently, the calibration sets are approximate in nature, and the coverage probabilities (α, δ) involved in the uncertainty statement (9) are nominal levels. In contrast to this approach, the method of Knafl, Sacks, Spiegelman and Ylvisaker needs no asymptotic justification. However, the error due to interpolation from the grid G must be compensated by enlarging the width of the confidence band, so their procedure is obviously designed to be conservative: the actual coverage probabilities exceed the nominal levels. Simulation studies are necessary to compare both procedures in terms of actual coverage probabilities and lengths of intervals.

We do not consider here the problems of bandwidth selection and bias correction that have to be made in practice. In the nonparametric regression setting, available methods for choosing h include minimization of an error criterion for the regression function. Ideally, in the calibration context, a more appropriate selection rule would be based on the mean squared error for the estimate $\hat{\xi}$ which is being considered or would be designed to minimize the length of the confidence intervals.

The proposed calibration method was also motivated by the desire to introduce robust estimation techniques into calibration. We have shown in Section 3 that the estimate $\hat{\xi}$ obtained from (3) with a bounded Ψ-function is robust in the minimax sense of Huber (1964). In practical applications, it seems likely that the robustness properties displayed in pointwise estimation will extend to the multiple-use case. From a theoretical point of view, the meaning of robustness in terms of asymptotic efficiency remains to be made precise in the multiple-use case.

APPENDIX

PROOF OF LEMMA 3. We show successively that the three last terms on the r.h.s. of (8) are negligible, uniformly in ξ.

(i) From the proof of Lemma 2 and Assumption (A6),

$$(nh)^{1/2} \sup_{\xi \in \mathcal{I}} |v^{-1}(\xi)\varepsilon_n(\xi)| = O\Big((nh)^{-1/2}(\log n)^2 |\Psi(\alpha_n)|\Big) \quad \text{a.s.}$$

(ii) To derive the uniform convergence in probability of $u_n(\xi) = (nh)^{1/2} v^{-1}(\xi) t_n(\xi)$ to 0, we first show that $u_n(\xi) \to 0$ in probability for all ξ,

which stems from Markov's inequality and assumption (M)(b). The tightness of the process u_n is a consequence of the moment condition $E(u_n(\xi_1) - u_n(\xi_2))^2 \le C|\xi_1 - \xi_2|^2$, where C is a constant, which is proved by standard arguments.

(iii) It remains to show that $h^{1/2}\sup_{\xi\in\mathscr{F}}|(v^{-1} - v_n^{-1})(\xi)\rho_n(\xi)| \to 0$ in probability. Let $h = n^{-\beta}$. Applying the result of Lemma 1 together with assumptions (A6) and (M)(b) we can write $h^{1/2}\sup_{\xi\in\mathscr{F}}|(v^{-1} - v_n^{-1})(\xi)\rho_n(\xi)| \le O((\log n)^{1/2}n^{-\beta})$, which tends to 0. □

PROOF OF PROPOSITION 3. First note that

$$H_n(\xi, Z_j) = H_n\big(\xi, r(\xi_j)\big) - g_n(\xi_j)e_j.$$

Then,

$$\begin{aligned}\mathrm{P}\{\mathscr{C}(Z_j) \ni \xi_j\} &= \mathrm{P}\Big(\big(g_n(\xi_j)\big)^{-1}|H_n(\xi_j, Z_j)| \le c\Big)\\ &= \mathrm{P}\Big(\Big|e_j - \big(g_n(\xi_j)\big)^{-1}H_n\big(\xi_j, r(\xi_j)\big)\Big| \le c\Big).\end{aligned}$$

Given $\mathscr{E} = \{(X_i, Y_i),\ i = 1, \dots, n\}$, we find

$$\begin{aligned}&\mathrm{P}\Big(\big(g_n(\xi_j)\big)^{-1}|H_n(\xi_j, Z_j)| \le c \,\Big|\, \mathscr{E}\Big)\\ &\qquad \ge \mathrm{P}\Big(-c + \big(g_n(\xi_j)\big)^{-1}\big|H_n\big(\xi_j, r(\xi_j)\big)\big|\\ &\qquad\qquad \le e \le -\big(g_n(\xi_j)\big)^{-1}\big|H_n\big(\xi_j, r(\xi_j)\big)\big| + c \,\Big|\, \mathscr{E}\Big)\\ &\qquad = 2\chi\Big(c - \big(g_n(\xi_j)\big)^{-1}\big|H_n\big(\xi_j, r(\xi_j)\big)\big|\Big) - 1.\end{aligned}$$

Thus, to satisfy (9) as $n \to \infty$, we choose $c > 0$ such that

$$\mathrm{P}\Big\{\inf_{\xi\in J}\chi\Big(c - (nh)^{-1/2}\lambda^{1/2}v^{1/2}(\xi)\big(g_n(\xi)\big)^{-1}|D_n(\xi)|\Big) \ge 1 - \frac{\alpha}{2}\Big\} \ge 1 - \delta \tag{10}$$

where

$$D_n(\xi) = (nh)^{1/2}\frac{H_n(\xi) - H(\xi)}{\lambda^{1/2}v^{1/2}(\xi)}$$

is the normalized deviation of H_n from H studied in Section 2 and $H_n(\xi) = H_n(\xi, r(\xi))$. It is a well known result that $\sup_{\mathscr{F}}|g_n(\xi) - g(\xi)| = O_P((nh)^{-1/2}(\log h^{-1})^{1/2})$. Therefore, $(nh)^{-1/2}v^{1/2}(\xi)g_n^{-1}(\xi)D_n(\xi)$ and $(nh)^{-1/2}v^{1/2}(\xi)g^{-1}(\xi)D_n(\xi)$ have the same limiting distribution. c can be chosen such that

$$\mathrm{P}\left\{\inf_{\xi}\left(c - \frac{\lambda^{1/2}v^{1/2}(\xi)}{(nh)^{1/2}g(\xi)}|D_n(\xi)|\right) \ge \chi^{-1}\Big(1 - \frac{\alpha}{2}\Big)\right\} \ge 1 - \delta.$$

Since we consider the case of homoscedastic errors, $(g(\xi))^{-1}v(\xi) = s^2, \forall \xi \in \mathscr{S}$. Then the uncertainty statement (9) will be established with a choice of c satisfying

$$\mathrm{P}\left\{ \left(2\log h^{-1}\right)^{1/2}\left(\sup_{\xi\in\mathscr{S}} |D_n(\xi)| - d_n \right) \right.$$
$$\left. \le \left(2\log h^{-1}\right)^{1/2}\left(\frac{(nh)^{1/2}}{\lambda^{1/2}s} g_0^{1/2}\left(c + \sigma\chi_0^{-1}\left(\frac{\alpha}{2}\right)\right) - d_n \right)\right\} = 1 - \delta$$

if $g \equiv g_0$ on the subinterval of future calibrations. Proposition 3 now follows from Lemma 3. □

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REFERENCES

BICKEL, P. and ROSENBLATT, M. (1973). On some global measures of the deviations of density function estimates. *Ann. Statist.* **1** 1071–1095.

CARROL, R., SPIEGELMAN, C. and SACKS, J. (1988). A quick and easy multiple-use calibration-curve procedure. *Technometrics* **30** 137–141.

CLARK, R. (1975). A calibration curve for radiocarbon dates. *Antiquity* **49** 251–266.

CLARK, R. (1979). Calibration, cross-validation and carbon-14. I. *J. Roy. Statist. Soc. Ser. A* **142** 47–62.

CLARK, R. (1980). Calibration, cross-validation and carbon-14. II. *J. Roy. Statist. Soc. Ser. A* **143** 177–194.

FINNEY, D. (1978). *Statistical Method in Biological Assay*. Griffin, London.

GRUET, M.-A. (1992). Analyse statistique de la calibration. Ph.D. thesis, Univ. Paris XI, Orsay.

HALL, P., KAY, J. and TITTERINGTON, D. (1990). Asymptotically optimal difference-based estimation of variance in nonparametric regression. *Biometrika* **77** 521–528.

HÄRDLE, W. (1989). Asymptotic maximal deviation of m-smoothers. *J. Multivariate Anal.* **29** 163–179.

HÄRDLE, W. and GASSER, T. (1984). Robust non-parametric function fitting. *J. Roy. Statist. Soc. Ser. B* **46** 42–51.

HUBER, P. (1964). Robust estimation of a location parameter. *Ann. Math. Statist.* **35** 73–101.

HUBERT, J. (1992). *Bioassay*. Kendall/Hunt, Dubuque, IA.

KNAFL, G., SACKS, J., SPIEGELMAN, C. and YLVISAKER, D. (1984). Nonparametric calibration. *Technometrics* **26** 233–242.

LECHNER, J., REEVE, C. and SPIEGELMAN, C. (1982). An implementation of the Scheffé approach to calibration using spline functions, illustrated by a pressure-volume calibration. *Technometrics* **24** 229–234.

LIERO, H. (1982). On the maximal deviation of the kernel regression function estimate. *Math. Operationsforsch. Statist.* **2** 171–182.

MACK, Y. and SILVERMAN, B. (1982). Weak and strong uniform consistency of kernel regression estimates. *Z. Wahrsch. Verw. Gebiete* **61** 405–415.

MEE, R., EBERHARDT, K. and REEVE, C. (1991). Calibration and simultaneous tolerance intervals for regression. *Technometrics* **33** 211–219.
MÜLLER, H. and SCHMITT, T. (1988). Kernel and probit estimates in quantal bioassay. *J. Amer. Statist. Assoc.* **83** 750–759.
NADARAYA, E. (1964). On estimating regression. *Theory Probab. Appl.* **9** 141–142.
OSBORNE, C. (1991). Statistical calibration: a review. *Int. Statist. Rev.* **59** 309–336.
ROSENBLATT, M. (1952). Remarks on a multivariate transformation. *Ann. Math. Statist.* **23** 470–472.
SCHEFFÉ, H. (1973). A statistical theory of calibration. *Ann. Statist.* **1** 1–37.
SILVERMAN, B. (1976). On a gaussian process related to multivariate probability density estimation. *Math. Proc. Cambridge Philos. Soc.* **80** 135–144.
TUSNADY, G. (1977). A remark on the approximation of the sample d.f. in the multidimensional case. *Period. Math. Hungar.* **8** 53–55.
WATSON, G. (1964). Smooth regression analysis. *Sankhyā Ser. A* **26** 359–372.

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