Maximally Selected Rank Statistics for Dose-Response Problems

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SUMMARY: We consider the bivariate situation of some quantitative, ordinal, binary or censored response variable and some quantitative or ordinal exposure variable (dose) with a hypothetical effect on the response. Data can either be the outcome of a planned dose-response experiment with only few dose levels or of an observational study where, for example, both exposure and response variable are observed within each individual. We are interested in testing the null hypothesis of no effect of the dose variable vs. a dose-response function depending on an unknown 'threshold' parameter. The variety of dose-response functions considered ranges from no observed effect level (NOEL) models to umbrella alternatives.

Here we discuss generalizations of the method of **Lausen & Schumacher (Biometrics, 1992, 48, 73-85)** which are based on combinations of two-sample rank statistics and rank statistics for trend. Our approach may be seen as a generalization of a proposal for change-point problems. Using the approach of **Davies (Biometrika, 1987, 74, 33-43)** we derive and approximate the asymptotic null distribution for a large number of thresholds considered. We use an improved Bonferroni inequality as approximation for a small number of thresholds considered. Moreover, we analyse the small sample behaviour by means of a Monte-Carlo study. Our paper is illustrated by examples from clinical research and epidemiology.

Keywords: Changepoint problem; Dose-response problem; Improved Bonferroni inequality; Logrank test; Maximally selected rank statistics; Threshold; Trend test; Upcrossing.

1 Introduction

The statistical analysis of dose-response relationships involves various aspects. Methods may be characterised by the measurement scales involved, by the functional form of the considered relationships and by the study design. We assume a general bivariate situation of some quantitative, ordinal, binary or censored response variable and some quantitative or ordinal dose variable with a hypothetical effect on the response. Figure 1 shows three different functional forms which are discussed in our paper:

(a) A simple cutpoint model, where an unknown cutpoint defines a normal and a risk population. The functional relationship is monontone, but not continuous.

(b) A monotone and continuous relationship, which is also characterised by a threshold. The model assumes no effect below the threshold and a monontone increase is assumed above the threshold. Consequently, the threshold can be seen as a non observed effect level (NOEL) and the model is called NOEL model.

(c) A monotone increase is assumed below a certain threshold in the dose variable and a decrease is assumed above this value. This continuous model is often called an umbrella type model and the threshold umbrella point.

Our approach covers also the mirrored model situations which can be defined by multiplying the response and/or dose variable by -1. But we do not discuss an analysis of one side of the umbrella model only (cf. Simpson & Margolin, 1986) or models which involve more than one structural parameter (cutpoint, NOEL, umbrella point or change-point); e.g. a simple example of such a model is the epidemic wave model (Siegmund 1986, Sec. 3.6.). Recently Chuang-Stein & Agresti (1997) reviewed traditional tests for detecting a monotone dose-response relationship with ordinal response data, which are based on general correlation or association statistics.

Figure 1 - about here -

Here, we discuss the three possibilities (i, ii, iii) of designs for dose-response modelling:
(i) controlled planned experiment with a dose or treatment variable;
(ii) randomly observed exposure values;
(iii) cumulative doses over time.
Under design (ii) and (iii) a continuous dose variable may result in a large number of possible thresholds. Consequently, we can model the threshold selection as stochastic process and we investigate a modification of the method of maximally selected rank statistics (section 3). We derive and propose approximations of the asymptotic distribution when there is no effect on the response variable. In section 4 we analyse the small sample behaviour by means of a Monte-Carlo simulation. Further below we analyse two examples: (section 5.1.) the binary response in a case-control study on electromagnetic fields and risk of cancer in children (cf. Olsen et al., 1993; Schulgen et al., 1994) and (section 5.2.) the possibly censored recurrence free survival time as response variable in a clinical heart arrhythmia study

(Hohnloser et al., 1987).

We consider the bivariate sample $(X_1, Y_1), ..., (X_N, Y_N)$ of size N; i.e. stochastically independent bivariate observations. X denotes the dose or exposure and Y denotes the response. We state our model of a dose-response relation in terms of the conditional distribution function of the response Y given an exposure or dose level x; i.e.:

$$F_{Y|X=x}(y) = pr_{g(x)}(Y \leq y) \ , \tag{1}$$

where $F_{Y|X=x}$ denotes the conditional distribution function and $pr_{g(x)}$ the probability indexed by $g(x)$. This formulation allows a wide range of dose-response relationships. For example the location shift model of Lausen & Schumacher (1992) is given by $g(x) - g(x') = \theta$ with $x \leq \mu$ and $x' > \mu$ where μ denotes the cutpoint and θ the location difference.

The null hypothesis of no effect of the dose or exposure on the distribution of the response is stated by

$$F_{Y|X=x}(y) = F_{Y|X=x'}(y) \text{ , for all } \ y, x, x' \in I\!R \ . \tag{2}$$

The null hypothesis can also be reformulated as $g(x) = constant$ for all $x \in I\!R$.

2 Rank Tests on Dose-Response Relation

Maximally selected rank statistics proposed by Lausen & Schumacher to test the null hypothesis $g(x) = constant$ are based on a selection of linear rank statistics S_d

(cf. Hajek & Sidak, 1967, p.61):

$$S_d = \sum_{i=1}^{N} c_d(Q_i)a(R_i) \ , \tag{3}$$

where $R = (R_1, ..., R_N)$ denotes the rank vector of the response variable Y; $Q = (Q_1, ..., Q_N)$ the rank vector of the dose or exposure variable X; $a = (a(1), ..., a(N))$ is some score vector and $c_d = (c_d(1), ..., c_d(N))$ is a regressor vector depending on a threshold d. In the case of tied or censored observations, $a(i)$ denotes the midscores or the scores given by the logrank statistic. Avoiding higher order indices we use $a(R_i)$ and not a_{R_i}.

Lausen & Schumacher (1992) use a regressor vector c_d which describes a two sample rank statistic. We give three (A, B, C) wellknown examples for regressor vectors corresponding to the three models (a) - (c) (cf. figure 1):

(A) $c_d^A(i) = I_{\{x(Q^{-1}(i))>d\}}$, Q^{-1} being the antiranks of Q and $I_{\{x(i)\geq d\}}$ denoting an indicator function of the event. This leads to the two sample cutpoint model of Lausen & Schumacher (1992);

(B) $c_d^B(i) = (i - m_d)^+ I_{\{x(Q^{-1}(i))>d\}}$, where $m_d = N - \sum I_{\{x(Q^{-1}(i))>d\}}$, is a regressor vector which may be used for NOEL alternatives (cf. e.g. Cox, 1987, Ulm, 1991, Meister, 1994, Chen, 1999a, Hothorn, 1999, and Bender, 1999);

(C) $c_d^C(i) = (m_d - i)^2$ is plausible for umbrella alternatives (cf. Mack & Wolfe, 1982, Hettmansperger & Norton, 1987, and Chen, 1999b).

With $m_d = 0$ and Wilcoxon scores we observe that a special case of example (B) is the Spearman rank test for independence.

The dependence of the regressor vector on some threshold d allows us to analyse various dose-response alternatives. But assuming that the true threshold parameter μ is unknown we are interested in a formal test procedure of the dose-response relationship considered. Consequently, we apply the approach of Lausen & Schumacher (1992) and use the standardized linear rank statistic $T_d = (S_d - E(S_d|a, X))/(var(S_d|a, X))^{1/2}$. The maximally selected rank statistic $M(\epsilon_1, \epsilon_2)$ is defined as

$$M(\epsilon_1, \epsilon_2) = \max_{d \in [d_1, d_2]} |T_d| \ , \tag{4}$$

where $d_1 = F_N^{-1}(\epsilon_1)$, $d_2 = F_N^{-1}(\epsilon_2)$, F_N^{-1} denotes the inverse of the empirical distribution function of X and $0 < \epsilon_1 < \epsilon_2 < 1$ are arbitrarily chosen. A similar test statistic is suggested for change point problems in Lombard (1987, eq. 2.4. and 5.1.).

In the sequel we call a maximally selected rank statistic (eq. 4) with regressor vector (A) cutpoint statistic, with regressor vector (B) NOEL statistic and with regressor vector (C) umbrella type statistic.

3 Asymptotic Null Distribution

3.1 Large Number of Thresholds

Here the asymptotic is derived when the sample sizes converge to inifinity. For clarification we add the index N at the scores and the statistics, but not at the ranks and antiranks. We follow the derivation of Lausen & Schumacher (1992). Assuming that the scores are standardized, i.e. $\sum_{i=1}^{N} a_N(i) = 0$ and $\sum_{i=1}^{N} a_N(i)^2 = 1$, then, when $\max_{\{1 \leq i \leq N\}} a_N(i) \rightarrow 0$ as $N \rightarrow \infty$, the processes

$$B_N(t) = \sum_{i=1}^{[Nt]} a_N(R(Q^{-1}(i)))$$

converge in distribution to a standard Brownian Bridge B_0 (see Billingsley, 1968, pp.208-214). Since

$$\begin{aligned} S_{Nd} &= \sum_{i=1}^{N} c_d^A(Q_i) a_N(R_i) \\ &= \sum_{X_i \leq d} a_N(R_i) \\ &= \sum_{i=1}^{NF_N(d)} a_N(R(Q^{-1}(i))) \\ &= B_N(F_N(d)) \end{aligned}$$

it follows by (4) that $M_N(\epsilon_1, \epsilon_2)$ converges weakly to

$$\sup_{t \in [\epsilon_1, \epsilon_2]} |B_0(t)|/(t(1-t))^{1/2} \text{ as } N \rightarrow \infty.$$

An asymptotic approximation of the distribution function $F(b) = pr(M(\epsilon_1, \epsilon_2) \leq b)$ is given by Miller & Siegmund (1982, eq.8):

$$pr(M(\epsilon_1, \epsilon_2) \leq b) = \frac{4}{b}\varphi(b) + \left(1 - \frac{1}{b}\right) \log\left(\frac{\epsilon_2(1-\epsilon_1)}{(1-\epsilon_2)\epsilon_1}\right) \varphi(b) + o\left(\frac{\varphi(b)}{b}\right).$$

Here we go a step further and derive for NOEL regressors c_d^B the asymptotic distribution of the maximally selected rank statistic under the null hypothesis. The process T_d with c_d^B as regressor functions can be considered as a smooth form of the process T_d^A with regressors c_d^A. This relation carries over to the limit.

Let $c_d^B(j) = (j - m_d)^+ I_{\{x(Q^{-1}(j))>d\}}$, $m_d = N - \sum_i I_{\{x(Q^{-1}(i))>d\}}$ and $S_{Nd} = \sum_{i=1}^N c_d^B(Q_i) a_N(R_i)$. Then $S_{NF^{-1}(\rho)}$ converges weakly to $\int_\rho^1 B_0(t)dt$ as a function of ρ. Let $T_{Nd} = (S_{Nd} - E(S_{Nd}|a, X))/(Var(S_{Nd}|a, X))^{1/2}$ and for $0 < \epsilon_1 < \epsilon_2 < 1$ let $L_N(\epsilon_1, \epsilon_2) = \max_{d\in[d_1,d_2]} |T_{Nd}|$ where $d_i = F_N^{-1}(i)$, $i = 1, 2$. Then $L_N(\epsilon_1, \epsilon_2)$ converges in distribution to $sup_{\rho\in[\epsilon_1,\epsilon_2]} | \int_\rho^1 B_0(t)dt/var(\int_\rho^1 B_0(t)dt)^{1/2}|$ as $N \to \infty$ (for details see section 8.1.). The results of Davies (1987) then allow an estimate of the distribution of the limit statistic. A somewhat lengthy calculation (see section 8.2.) yields for $K(\epsilon_1, \epsilon_2) = \sup_{\rho\in[\epsilon_1,\epsilon_2]} | \int_\rho^1 B_0(t)dt/var(\int_\rho^1 B_0(t)dt)^{1/2}|$, that

$$pr(K(\epsilon_1, \epsilon_2) > c) \leq 2\left(\Phi(-c) + \frac{\varphi(c)}{(2\pi)^{1/2}} \int_{\epsilon_1}^{\epsilon_2} \left(\frac{12\rho}{(1-3\rho^2+2\rho)^2}\right)^{1/2} d\rho\right) \tag{5}$$

$$= 2\left(\Phi(-c) + \frac{\varphi(c)}{(2\pi)^{1/2}} \left[\tan^{-1}\left\{-(3t)^{1/2}\right\} - 3^{1/2}\tanh^{-1}\left\{-t^{1/2}\right\}\right]_{\epsilon_1}^{\epsilon_2}\right). \tag{6}$$

Table 1 gives $(1 - \alpha)$-quantiles of the approximation of the asymptotic distribution. For umbrella regressors c_d^C we can use a similar argument as for NOEL regressors twice and can derive an approximation via Davies (1987, eq.2.1) again.

- Table 1 - about here -

3.2 Small Number of Thresholds

The asymptotic k-variate normal distribution for k potential thresholds, $z_1, ..., z_k$ and $z_0 = -\infty$, $z_{k+1} = \infty$, considered is given by standard arguments, Noether condition (see above) and $(F_{NX}(z_{j+1}) - F_{NX}(z_j))\ N \to \infty$ for $j = 0, ..., k$ with $N \to \infty$. We approximate the asymptotic k-variate normal distribution with the improved Bonferroni inequality of Hunter and Worsley (Hunter, 1976; Worsley, 1982, 1983):

$$pr(M(\epsilon_1, \epsilon_2) \leq b) \approx 2(1 - \Phi(b)) + \textstyle\sum_{i=1}^{k-1} D(l_i, l_{i+1}),$$

where the realisation of $M(\epsilon_1, \epsilon_2)$ equals b, $z_1 < ... < z_k$ denotes the cutpoints which define the splits considered, l_i denotes the size of the subgroup with values in X less or equal to z_i, and we get $D(i, j) = (2/\pi)^{0.5}\varphi(b)\ (t_{ij} - (b^2/4 - 1)(t_{ij})^3/6)$, φ denotes the standard normal probability density function and Φ the standard normal distribution function (c.f. Worsley 1983, eq. 6.4.); for the cutpoint model regressors c_d^A we get for the correlation term $t_{ij} = (1 - i(n - j)/((n - i)j))^{0.5}$. Schlittgen (1999) suggests an exact computation based on the asymptotic k-variate normal distribution. The results of James et al. (1987) provide an other possibility to approximate the asymptotic k-variate normal distribution. Tang et al. (2000) discuss exact linear trend tests in dose-response studies.

4 Small sample behaviour

Koziol (1991) and Halpern (1999) suggest rapid methods to compute the permutation distribution for a binary response variable. We analyse the small sample behaviour by using results of a Monte-Carlo study for a continuous response variable. We use the design and adapt the programs of the study in Lausen & Schumacher (1992). Consequently we chose the uniform distribution for the dose X and the standard normal distribution for the response Y and 10000 Monte-Carlo replications (more details are given in Lausen & Schumacher 1992). We include three different NOEL statistics (Median-, Wilcoxon- and log-rank-scores) and one cutpoint statistics (maximally selected two-sample t-test, see Lausen & Schumacher 1992). The maximally selected two-sample t-test is included to allow comparisons with the simulation results of cutpoint statistics and is the best parametric cutpoint test statistic under our simulation design. The simulation results of Lausen & Schumacher (1992) show that the performance ot the maximally selected Wilcoxon test statistic and the maximally selected two-sample t-test is similar. For example one gains relatively little power by using the parametric statistic.

Figure 2a shows the upper part of the distribution of the simulated NOEL statistic with Wilcoxon scores for the interval (.1, .9) and for different sample sizes. Moreover, the approximation (eq. 5) of the asymptotic distribution is given. The figure shows that the approximation is conservative. Table 2 gives simulated and approximated ($n = \infty$) 95% quantiles for the sample sizes, intervals and test statistics considered under the null hypothesis. The given results underline, that the selection effect is smaller compared with the cutpoint statistic, and that the approximation formula (eq. 5) of the asymptotic distribution is conservative, but sharp enough to be useful.

Table 2 - about here -

Figure 2b-d gives the simulated power for three alternatives considered: NOEL model ($g(x) = \beta(x-\mu)I_{\{x\geq\mu\}}$, $\mu = 0.5$, β constant slope parameter), linear model ($g(x) = \beta x$, β constant slope parameter), and cutpoint model ($g(x) = \theta I_{\{x\geq\mu\}}$, $\mu = 0.5$, θ location difference). The sample size is $n = 50$. The effect parameter describes the slope of the linear part of the NOEL model, the slope of the linear model and the location difference of the cutpoint model. Figure 2b-d shows the simulated power for three different NOEL statistics (Median-, Wilcoxon- and log-rank-scores) and for the cutpoint statistic (maximally selected two-sample t-test). All tests use the simulated quantiles under the null hypothesis and the selection interval (.25, .75). We observe that the NOEL-statistics (Wilcoxon- and logrank-scores) have the highest power under the NOEL-model (figure 2b). Under the linear-model (figure 2c) the NOEL-statistic and the cutpoint statistic have a similar simulated power. Under the cutpoint model (figure 2d) the cutpoint statistic performs best.

Figure 2(a-d) - about here -

5 Examples

5.1 Electromagnetic Fields and Risk of Cancer in Children

Olsen et al. (1993) observed an association between the binary response occurence of all major types of childhood cancer and exposure to magnetic fields from high voltage installations. Table 3 gives the relevant data. This finding was based on an outcome-oriented cutpoint and on the maximally selected chi square statistic (Schulgen et al. 1994). But the continuous NOEL model is an alternative model of the dose-response relationship of average exposure to electromagnetic fields (unit μTesla) and risk of cancer in children. Figure 3 shows the process of the maximally selected chi square test statistics and the NOEL statistic with Wilcoxon scores. Having about 1 % exposed we can restrict the selection between the 99% and 99.9% quantiles of the exposure distribution; i.e. 0 μTesla to 0.51 μTesla. We get for the maximally selected qui square statistic 3.13 (P = 0.023) at the cutpoint 0.45 μTesla and for the NOEL statistic 3.27 (P = 0.004) at the cutpoint 0.45 μTesla. The continuous NOEL model is a better approximation of a plausible biological model (for more details see Schulgen et al. 1994). We observe only 6 cases and 2 controls above the threshold 0.45 μTesla, therefore interpretations of this finding have to be very cautious.

Table 3 - about here -

Figure 3 - about here -

5.2 Recurrence Free Survival in Heart Arrhythmia Study

The study of Hohnloser et al. (1987) shows that the left ventricular ejection fraction has some predictive power for patients with malignant ventricular arrhythmias. Lausen & Schumacher (1992, Table 1) provide a subset of the study data and an analysis using the cutpoint logrank statistic. Figure 4 gives the empirical processes of the NOEL-logrank statistic with a monotone increase for values greater than the threshold and of the NOEL logrank statistic with a monontone decrease for values less than the threshold. Moreover, the process of the cutpoint logrank statistics is shown. Restricting the selection between the 5 % and 95 % quantiles of the left ventricular ejection fraction we get for the NOEL-logrank statistic 3.69 (P = 0.001) with a monotone increase for values greater than the threshold, for the NOEL-logrank statistic 3.41 (P = 0.003) with a monotone decrease for values less than the threshold and for the cutpoint logrank statistic 3.61 (P = 0.012). The Spearman rank test for independence is a special case of the NOEL statistic (cf. section 2), consequently the pattern of the processes of figure 4 may be interpreted as an indication, that a strictly monotone relationship provides a better model for these data.

Figure 4 - about here -

6 Discussion

In this paper, we suggest and investigate a nonparametric statistical analysis of dose-response problems with maximally selected rank statistics. We introduce the approach for a large class of dose-response models and for different scales of the dose and response variable. We show that the asymptotic null distribution of the NOEL statistic is the supremum of the absolute value of the normalized integral over a Brownian bridge. Moreover, we derive an approximation formula for the asymptotic null distribution. Results of a Monte-Carlo study show that the approximation formula is sharp and the NOEL statistic is powerful under the NOEL model.

Contal & Quigley (1999) use a cutpoint model and investigate maximally selected logrank statistics with a Brownian Bridge asymptotic. Moreover, they discuss the effect of the amount of censoring and the prognostic value of age for breast cancer data of Institut Curie (Paris, France).

Rabinowitz & Betensky (2000) introduce maximally selected McNemar's statistics. Betensky & Rabinowitz (1999) discuss a cutpoint statistics for $K \times 2$ tables, prove that the asymptotic null distribution is a multidimensional Brownian bridge and give an approximation via results of James et al. (1987). It should be possible to extend our approach using results of Davies (1987) for chi-square statistics with k degrees of freedom to derive a similar approach for dose-response models of a multivariate response variable.

Concerning estimation of the threshold and effect parameters it should be noted that effect estimation conditional on the threshold estimation given by a maximally selected statistic is often biased (cf. Lausen & Schumacher 1996).

In summary our nonparametric approach is an improvement of the cutpoint model, because it allows the analysis of a monotone dose-response relation which is often a plausible model of the dose-response relation within a subject (cf. Schulgen et al. 1994). Such a nonparametric analysis is especially important, when we have not sufficient data, i.e. too much noise or unexplained variation, to support estimates of a specified parametric model or a data analysis, guided by smoothing techniques.

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8 Appendix

8.1 Convergence of the NOEL-statistic

Let $S_{Nd} = \sum_{i=1}^{N} c_d^B(Q_i) a_N(R_i)$ denote the statistic as introduced in section 3.1.. We rewrite S_{Nd}/N as a Rieman-integral. Let $D = R \circ Q^{-1}$, where R denote the ranks of Y and Q the ranks of X. Then we have

$$\begin{aligned}
S_{Nd}/N &= \sum_{i=1}^{N} c_d^B(Q_i)\ a_N(R_i)/N \\
&= \sum_{i=1}^{N} (Q_i - m_d)\ I_{\{X_i > d\}}\ a_N(R_i)/N \\
&= \sum_{j=1}^{N} (j - m_d)\ I_{\{X(Q_j^{-1}) > d\}}\ a_N(D_j)/N \\
&= \sum_{j=m_d+1}^{N} (j - m_d)\ a_N(D_j)/N \\
&= \sum_{j=m_d+1}^{N} \left(\sum_{i=m_d+1}^{j} a_N(D_j)/N \right)
\end{aligned}$$

By interchanging summation and noting that the a_N's are centered we get further

$$\begin{aligned}
S_{Nd}/N &= \sum_{i=m_d+1}^{N} \left(\sum_{j=i}^{N} a_N(D_j)/N \right) \\
&= \sum_{i=m_d+1}^{N} \left(\sum_{j=1}^{N} a_N(D_j)/N - \sum_{j=1}^{i-1} a_N(D_j)/N \right) \\
&= - \sum_{i=m_d+1}^{N} \sum_{j=1}^{i-1} a_N(D_j)/N \ .
\end{aligned}$$

We claim at first, that

$$H_N(\rho) := \sum_{i=[N\rho]+1}^{N} \sum_{j=1}^{i-1} a_N(D_j)/N$$

as a function of ρ converges to $\int_\rho^1 B_0(t)dt$ in $D[0,1]$. $D[0,1]$ denotes the usual Skorokhod-space (see Billingsley 1968, p. 109). This is a consequence of the fact mentioned above, that $B_N(t) = \sum_{i=1}^{[Nt]} a_N(D_i)$ converges weakly to a Brownian bridge $B_0(t)$ in $D[0,1]$. For $x \in D[0,1]$ denote by $T(x)$ the function $\rho \to \int_\rho^1 x(s)ds$. T defines a mapping from $D[0,1]$ to $C[0,1]$ ($C[0,1]$ denotes as usual the space of continuous functions on $[0,1]$). T is a continuous mapping when restricted on $C[0,1]$. Since the Brownian bridge has continuous pathes with probability one, we obtain by a classical convergence result for mappings (see Billingsley 1968, p. 30) that $T(B_N)$ converges to $T(B_0)$ in distribution in $C[0,1]$. Further it holds that

$$r_N := \sup_\rho |T(B_N)(\rho) - H_N(\rho)| \ \to \ 0 \tag{7}$$

in probability as $N \to \infty$. This yields the first claim. We show now that $S_{NF^{-1}(\rho)}/N$ as a function of ρ converges to $\int_\rho^1 B_0(t)dt$ in $D[0,1]$. Since $m_d = NF_N(d)$, (F_N denotes the empirical distribution function of X) we have

$$S_{NF^{-1}(\rho)}/N = H_N(F_N(F^{-1}(\rho)))$$

then we get by the triangle inequality

$$\begin{aligned}
\sup_\rho \ | \ & H_N(F_N(F^{-1}(\rho))) - H_N(\rho)| \\
\leq \ & \sup_\rho |\int_{F_N(F^{-1}(\rho))\wedge\rho}^{F_N(F^{-1}(\rho))\vee\rho} B_N(t)dt| + 2r_N \\
\leq \ & \sup_\rho |F_N(F^{-1}(\rho)) - \rho| \sup_{0\leq t\leq 1} |B_N(t)| + 2r_N \ .
\end{aligned}$$

The second term converges to zero by (7). The first term also does. The first factor converges to zero by the Clivenko-Cantelli lemma. The second term stays bounded in probability by the tightness of B_N. This shows the second claim.

The other statements follow by similar standard arguments.

8.2 *The asymptotic approximation of Davies*

We consider the limit functional $Z(\rho) := \int_\rho^1 B_0(t)dt$ where B_0 is a standard Brownian bridge on the interval $[0,1]$. As a function of ρ it is a Gaussian process with absolut continuous paths and zero mean. Its covariance function is given by $v(\rho,\rho') := cov(Z(\rho), Z(\rho')) = (1/12)(1-\rho')^2(1-3\rho^2+2\rho')$ when $\rho \le \rho'$.

This can be seen as following:

Since $E(Z(\rho)) = 0$ for all $0 \le \rho \le 1$

$$\begin{aligned} v(\rho,\rho') &= E(\int_\rho^1 \int_{\rho'}^1 B_0(t)B_0(t')dtdt') \\ &= \int_\rho^1 \int_{\rho'}^1 E(B_0(t)B_0(t'))dtdt' \\ &= \int_\rho^1 \int_{\rho'}^1 (t \wedge t')(1 - t \vee t')dtdt' \end{aligned}$$

The calculation of the integral on the right hand side yields the expression for the covariance function.

Let $\kappa(\rho,\rho')$ denote the correlation function of $Z(\rho)$. The second partial derivative can be calculated as

$$\partial^2_{\rho'}\kappa(\rho,\rho')|_{\rho=\rho'} = \frac{-12\rho}{(1-3\rho^2+2\rho)^2} \ .$$

Together with the result of Davies (1987) (eq. 2.1.) this leads to the right hand side of formula (5) above, which turns out to coincide with formula (6).

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10 *Legends*

Figure 1: Typical functional forms of dose-response relationships.

Cutpoint model (solid line), no observed effect level model (NOEL) (dotted line), umbrella type model (dashed and dotted line).

Figure 2: Small sample behaviour.

Under the null hypothesis:

(2a) Upper part of the distribution of simulated NOEL statistic with Wilcoxon scores for the selection interval (.1, .9).

Under the dose-reponse alternatives:

(2b) NOEL model, (2c) linear model, (2d) cutpoint model.

Figure 3: Average exposure and risk of cancer in children.

Process of NOEL statistic with Wilcoxon scores (dotted and dashed line), and process of maximally selected chi square statistic (solid line). Selection between 0 μTesla (99% quantile) and 0.51 μTesla (99.9% quantile.

Figure 4: Left ventricular ejection fraction and recurrence free survival time.

Process of the NOEL-logrank statistic with monotone decrease for values less than the threshold (dotted and dashed line), with monotone increase for values greater than the threshold (dashed line), and process of cutpoint logrank statistic (solid line).

11 *Tables*

Table 1: Approximated (1 - α) quantiles of asymptotic distribution.

		(1 - α) quantiles of asymptotic distributions					
	absolute	asymptotic quantile for interval					
α	normal	(.4, .6)	(.25, .75)	(.1, .9)	(.05, .95)	(.01, .99)	(.4, .9)
.100	1.645	1.784	1.957	2.134	2.220	2.358	2.073
.050	1.960	2.097	2.261	2.424	2.503	2.630	2.368
.025	2.241	2.376	2.532	2.686	2.759	2.877	2.633
.010	2.576	2.708	2.856	2.999	3.067	3.176	2.950

Table 2: Simulated and approximated 95 % quantiles.

ϵ_1	ϵ_2	n	t	noel-Med	noel-Wilc	noel-LR
0.4	0.6	10	2.90	2.16	2.00	1.93
0.4	0.6	20	2.59	2.08	2.04	2.01
0.4	0.6	30	2.56	2.07	2.08	2.06
0.4	0.6	50	2.55	2.14	2.12	2.11
0.4	0.6	100	2.55	2.11	2.14	2.11
0.4	0.6	200	2.55	2.12	2.12	2.10
0.4	0.6	∞	2.56	2.10	2.10	2.10
0.25	0.75	10	3.38	2.16	2.11	2.10
0.25	0.75	20	2.95	2.23	2.14	2.13
0.25	0.75	30	2.89	2.20	2.20	2.18
0.25	0.75	50	2.81	2.21	2.22	2.19
0.25	0.75	100	2.76	2.24	2.24	2.22
0.25	0.75	200	2.79	2.22	2.23	2.24
0.25	0.75	∞	2.83	2.26	2.26	2.26

ϵ_1	ϵ_2	n	t	noel-Med	noel-Wilc	noel-LR
0.1	0.9	10	3.66	2.16	2.09	2.20
0.1	0.9	20	3.22	2.23	2.25	2.29
0.1	0.9	30	3.10	2.21	2.28	2.30
0.1	0.9	50	3.01	2.31	2.32	2.34
0.1	0.9	100	3.01	2.36	2.38	2.40
0.1	0.9	200	2.96	2.36	2.38	2.38
0.1	0.9	∞	3.05	2.42	2.42	2.42
0.4	0.9	10	3.32	2.16	2.06	2.13
0.4	0.9	20	3.00	2.20	2.20	2.24
0.4	0.9	30	2.89	2.21	2.24	2.28
0.4	0.9	50	2.83	2.24	2.26	2.28
0.4	0.9	100	2.83	2.31	2.33	2.34
0.4	0.9	200	2.86	2.33	2.35	2.36
0.4	0.9	∞	2.88	2.37	2.37	2.37

Table 3: Danish population based case control study: Average exposure.

	cases	controls
Non exposed (Exposure = 0 μT)	1693	4750
Exposed (Exposure > 0 μT)	14	38
total	1707	4788

Ordered exposure values (μT) of cases
0.03, 0.04, 0.04, 0.08, 0.12, 0.12, 0.20, 0.21, 0.51, 0.73, 1.00, 1.59, 1.66, 1.72;

Ordered exposure values (μT) of controls
0.03, 0.04, 0.04, 0.04, 0.04, 0.04, 0.04, 0.05, 0.05, 0.06, 0.06, 0.06, 0.06, 0.07, 0.07, 0.08, 0.08, 0.09, 0.14, 0.15, 0.15, 0.17, 0.19, 0.20, 0.21, 0.23, 0.24, 0.28, 0.30, 0.30, 0.30, 0.32, 0.32, 0.34, 0.35, 0.45, 0.73, 0.83;