Efficient multivariate inference in general factorial diagnostic studies

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Abstract

We propose new simultaneous inference methods for diagnostic trials with elaborate factorial designs. Instead of the commonly used total area under the receiver operating characteristic curve, we focus on partial areas under the curve as parameters of interest. We construct a nonparametric multiple contrast test for these parameters and show that it asymptotically controls the family-wise type one error rate. Finite sample properties of this test are investigated in a series of computer experiments. We provide empirical and theoretical evidence supporting the conjecture that statistical inference about partial areas under the curve is more efficient than inference about the total area under the curve.

Keywords: partial AUC, trimmed Mann–Whitney statistic, empirical processes

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1. Introduction

Modern medicine can rely on a variety of diagnostic biomarkers ranging from imaging techniques over gene expression measurements to classical laboratory parameters like antibody concentration in a blood sample. Given their ability to detect diseases or disease-related complications at ever earlier stages, they are indispensable in today’s clinical practice. Yet, before a biomarker can be admitted for use, its reliability must be ascertained in a series of diagnostic studies so as to satisfy the high standards of contemporary evidence-based medicine.

Many biomarker measurements produce values on continuous or discrete scales. In order to yield a binary diagnostic decision, the clinical practitioner usually compares the observed marker value to a disease-defining threshold. Subjects with marker values exceeding this threshold will then receive a positive diagnosis. Of course, when we evaluate the marker’s viability in a diagnostic study, we do not yet know the optimal choice for the disease-defining threshold. To characterize the marker’s performance independently of the specific threshold, we consider the receiver operating characteristic (ROC) curve. For each possible threshold value \(t\), the marker has a probability of assigning a positive diagnosis correctly (true positive probability, \(TPP(t)\)) and a probability of doing so incorrectly (false positive probability, \(FPP(t)\)). With \(t\) ranging over \(\mathbb{R}\), the ROC curve aggregates all the points \((FPP(t), TPP(t))\). The degree to which the resulting curve is attracted by the point \((0, 1)\) characterizes the marker’s diagnostic reliability—the area under the curve (AUC) is therefore a popular parameter of interest in diagnostic trials.

A typical diagnostic trial examines the reliability of biomarkers at different levels of several experimental factors. For instance, we might want to compare two MRI imaging biomarkers, each of which is interpreted by several different readers. A primary objective is then to uncover the existing main and interaction effects of these factors on the parameter of interest. Statistically, this leads to the problem of testing a family of linear hypotheses [11]. Multiple contrast tests are a tailor-made technique for this type of problem. They are designed to simultaneously test several linear hypotheses while keeping the family-wise type I error rate at the desired level. Being considerably more flexible and less conservative than traditional approaches based on p-value corrections [4, 11, [12], they seem like an ideal method to consider for the statistical analysis of...
factorial diagnostic studies. It was only recently, though, when Konietschke et al. [11] first implemented the multiple contrast test in this context. Based on nonparametric estimators, they constructed multiple contrast tests for AUCs of diagnostic markers in general factorial diagnostic studies. Further developments were due to Blanche et al. [3]. Thus, the possibilities for nonparametric statistical inference about biomarker AUCs in diagnostic trials have greatly improved over the last years.

Popular though it may be, using the AUC as a performance measure of diagnostic markers has a serious drawback. Even in the simple case of comparing just two markers in terms of their AUCs, the picture can get quite ambiguous if the corresponding ROC curves cross each other [20]. In this case, the advantage that one marker may enjoy over the other at moderate threshold values might be offset by the reverse situation at more extreme thresholds, such that both AUCs can be of comparable magnitude even if the ROC curves are rather distinctly shaped. In clinical applications extreme threshold values would most certainly be avoided because they risk an unbearable decrease of the true positive or increase of the false positive probability, and so the marker that is superior for moderate $t$ would be preferable from this perspective. However, the two AUCs being statistically unintelligible, the superior properties of that marker would not be recognized.

To circumvent such inefficiencies, we should focus our statistical analysis on the clinically relevant segments of the ROC curves. Many authors have proposed to define these segments via upper and lower boundaries for the false positive probability [2, 6, 14, 16, 25, 28, 29]. However, the benefits of this idea in terms of increased efficiency is questionable [27]. In a novel approach, Yang et al. [27] defined the clinically relevant segment by setting a lower bound for the true positive probability and an upper bound for the false positive probability. We can then use a suitably defined area under the resulting ROC curve segment to assess and compare biomarkers in clinically relevant settings; to refer to this parameter, we use the term *partial area under the ROC curve* (partial AUC).

Nonparametric statistical inference about partial AUCs has heretofore only been considered by Yang et al. [27] for pairwise comparisons. Techniques for multiple comparisons of partial AUCs that would enable their use as parameters of interest in diagnostic studies with elaborate factorial designs are still lacking. In this article we will close this gap by showing that the multiple contrast test principle can be successfully applied in connection with a nonparametric estimator of the partial AUC. To this end, we derive the asymptotic distribution of this estimator in a general multivariate setting and show that we can consistently approximate its distribution using Efron's bootstrap. We do not make any assumption on the underlying distribution of the observed marker values or their covariance structure. As a result, we can present an asymptotically correct nonparametric multiple contrast test procedure for simultaneously testing families of arbitrary linear hypotheses about partial AUCs. We will also show analytically and numerically that multiple inference about partial AUCs in clinical studies may indeed be more efficient than the established methods based on the total AUC.

In Section 2 we will formally introduce the partial AUC as a statistical parameter and define a multiple testing problem about it. In Section 3 we introduce a nonparametric estimator of the partial AUC and construct a family of statistical tests for the aforementioned multiple testing problem. Section 4 states important theoretical results regarding the asymptotic properties of the proposed estimator and test family, including the estimator's asymptotic distribution and the test family's ability to asymptotically control the family-wise type I error rate. In Section 5 we present the results of a series of computer experiments in which we examined the finite sample properties of our test and tried to empirically corroborate our conjecture that inference about the partial AUC is more efficient than inference about the total AUC. We also provide theoretical arguments in support of this conjecture.

### 2. The statistical model—parameters and hypotheses

In this paper we focus on diagnostic trials in which the same population of subjects supplies the marker observations at each combination of factor levels. The typical example is a multi-reader trial comparing several biomarkers, where each subject's marker measurements are interpreted by a fixed number of different readers. A standard assumption in the modelling of diagnostic trials is furthermore the availability of a diagnostic gold standard allowing us to divide the population of participating subjects into two subgroups, one
of a non-diseased subjects and one of $\beta$ diseased subjects. If we have a total of $\kappa$ factor level combinations, we end up with the following statistical model. Corresponding to each factor level combination $i \in \{1, \ldots, \kappa\}$, we have a distribution of marker values in the population of diseased subjects, $P_i^{(1)}$, and accordingly a distribution of marker values in the population of non-diseased subjects, $P_i^{(0)}$. For each non-diseased subject $r \in \{1, \ldots, \alpha\}$, we observe $\kappa$ different marker values which we aggregate in a $\kappa$-dimensional real vector. This vector is interpreted as the realization of a random vector $\xi_r = (\xi_r(1), \ldots, \xi_r(\kappa))$ whose marginal distributions are $P_i^{(0)}, \ldots, P_i^{(0)}$. Analogously, the observed marker values in a diseased subject $s \in \{1, \ldots, \beta\}$ are realizations of a random vector $\eta_s = (\eta_s(1), \ldots, \eta_s(\kappa))$ with marginals $P_1^{(1)}, \ldots, P^{(1)}$. While it is reasonable to assume that $\sigma(\xi_{1}, \ldots, \xi_{\alpha})$ and $\sigma(\eta_{1}, \ldots, \eta_{\beta})$ are independent [11, 13], we do not impose any assumption regarding the structure of the distributions $P^{(1)}$ and $P^{(0)}$, making the model entirely nonparametric. We summarize our model assumptions in Definition 1.

**Definition 1.** We consider two sequences of random vectors, $[\xi_r]_{r \in \mathbb{N}_+}$ and $[\eta_s]_{s \in \mathbb{N}_+}$, with $(\xi_r(1), \ldots, \xi_r(\kappa)) \sim P^{(0)}$ and $(\eta_s(1), \ldots, \eta_s(\kappa)) \sim P^{(1)}$. The cumulative distribution functions of $P^{(0)}$ and $P^{(1)}$ are denoted by $F$ and $G$, respectively. Let $P^{(0)}$ and $P^{(1)}$ be the marginal distributions of $\xi_r(i)$ and $\eta_s(i)$, respectively, and let $F_i$ and $G_i$ denote the corresponding cumulative distribution functions. We assume that $\sigma(\xi_r : r \in \mathbb{N}_+)$ and $\sigma(\eta_s : s \in \mathbb{N}_+)$ are independent for $\alpha, \beta \in \mathbb{N}_+$, our observations are realizations of $\xi_1, \ldots, \xi_\alpha$ and $\eta_1, \ldots, \eta_\beta$.

For each combination of factor levels, we have a ROC curve $\varphi_i$ characterizing the corresponding marker performance. These curves are formally given by the parametrization $\varphi_i = \{\varphi_i(t) = (1 - F_i(t), 1 - G_i(t)) : t \in \mathbb{R}\}$. Following Yang et al. [27], we define the clinically relevant segments of the curves $\varphi_i$ by stipulating a maximal acceptable false positive probability $p$ and a minimal acceptable true positive probability $q$. The relevant segment of $\varphi_i$ is then the collection of all points $\varphi_i(t)$ satisfying $1 - F_i(t) \leq p$ and $1 - G_i(t) \geq q$. A graphical illustration is given in Figure 1. The partial area under $\varphi_i$ that defines the parameter of our interest is the area surrounded by the curves

$$C_{i,1} = \{(1 - F_i(t), 1 - G_i(t)) : F_i^{-1}(1 - p) \leq t \leq G_i^{-1}(1 - q)\},$$

$$C_{i,2} = \{(t, q) : 1 - F_i(G_i^{-1}(1 - q)) \leq t \leq p\},$$

$$C_{i,3} = \{(p, t) : q \leq t \leq 1 - G_i(F_i^{-1}(1 - p))\},$$

implicitly presupposing that $F_i$ and $G_i$ are continuous and strictly increasing.

In some sense the partial area under the curve is a scaled down version of the total area under the curve and therefore its natural extension to boundaries $q > 0$ or $p < 1$. With Green’s Theorem we infer that the so
defined area is equal to
\[ \int_{(a,b)} (G_i(b) - G_i(u)) \, dF_i(u), \]
with \( a = F_i^{-1}(1 - p) \) and \( b = G_i^{-1}(1 - q) \). Using the notion of the generalized quantile function \( H^{-1}(p) = \inf\{t \in \mathbb{R} : H(t) \geq p\} \) of a distribution function \( H \), the expression in the preceding display is also well defined for piecewise constant functions with jumps. We will therefore use it to formally define multivariate area under the curve parameters. In the following, for any \( q \in \mathbb{N}_+ \), \( \{e_1, \ldots, e_q\} \) denotes the canonical basis and \( \langle \cdot, \cdot \rangle \) the standard inner product in \( \mathbb{R}^q \).

**Definition 2.** For \( p, q \in (0, 1) \) and \( i \in \{1, \ldots, k\} \), we define \( a_i = F_i^{-1}(1 - p) \) and \( b_i = G_i^{-1}(1 - q) \). We additionally assume that for some \( \varepsilon > 0 \) each \( F_i \) and \( G_i \) is continuously differentiable in \( (a_i - \varepsilon, a_i + \varepsilon) \cup (b_i - \varepsilon, b_i + \varepsilon) \).

Their derivatives at a point \( t \) are denoted \( \partial_x F_i(x) = f_i(x) \) and \( \partial_x G_i(x) = g_i(x) \), respectively, and we assume that \( f_i(a_i) \wedge g_i(a_i) \wedge f_i(b_i) \wedge g_i(b_i) > 0 \). The partial area under the curve parameter of the pair of distributions \( \{P^{(0)}, P^{(1)}\} \) is

\[ \theta_{p,q} = \sum_{i=1}^k e_i \int_{(a_i,b_i)} (G_i(b_i) - G_i(u)) \, dF_i(u). \]

With a slight abuse of notation, we shall denote with \( \theta_{1,0}[P] \) the total area under the curve parameter given by

\[ \theta_{1,0}[P] = \sum_{i=1}^k e_i \int_{\mathbb{R}} (1 - G_i(u)) \, dF_i(u). \]

In this case, we drop the additional assumptions on the marginal distribution functions \( F_i, G_i \). Specifically we have to acknowledge that \( \lim_{x \to -\infty} f_i(x) = \lim_{x \to -\infty} g_i(x) = 0 \). Henceforth, whenever we use the notation \( \theta_{p,q} \) or canonical forms of it, we implicitly mean \( p, q \in (0, 1) \). When referring to the case \( (p, q) = (1, 0) \), we shall always do so explicitly.

Under the assumption that \( \sigma(\eta_1, \ldots, \eta_p) \) and \( \sigma(\xi_1, \ldots, \xi_q) \) are independent, a well known representation of the total area under the curve is \( \theta_{0,1} = \sum_{i=1}^k \Pr[\xi(i) < \eta_1(i)] \). A similar relation holds for the partial area under the curve. Presupposing again independence of the diseased and non-diseased populations, we see that

\[ \theta_{p,q} = \sum_{i=1}^k e_i \Pr[a_i < \xi_1(i) < \eta_1(i) \leq b_i]. \]

Furthermore, the partial AUC is invariant under monotone transformations. For a strictly increasing real function \( m \), let \( F_{m(\xi_1(i))} \) and \( G_{m(\eta_1(i))} \) be the distribution function of \( m(\xi_1(i)) \) and \( m(\eta_1(i)) \), respectively. Then \( F_i(t) = F_{m(\xi_1(i))}(m(t)) \), \( G_i(t) = G_{m(\eta_1(i))}(m(t)) \), and

\[ \Pr[F_i^{-1}(1 - p) < \xi_1(i) < \eta_1(i) \leq G_i^{-1}(1 - q)] = \Pr[F_i^{-1}(m(\xi_1(i)))(1 - p) < m(\xi_1(i)) < m(\eta_1(i)) \leq G_i^{-1}(m(\eta_1(i))(1 - q))] \].

What kind of statistical hypotheses about the parameter \( \theta_{p,q} \) are we likely to face in a diagnostic study? Perhaps the most frequently posed research questions in the context of factorial experiments concern the presence of main and interaction effects of the involved factors on the parameter of interest. Other examples include Dunnett-type many-to-one comparisons, where we compare each treatment to a fixed reference treatment, or Tukey-type all pairs comparisons, where we conduct a series of pairwise comparisons between treatments. All of those examples have in common that they lead to multiple testing problems involving families of linear hypotheses, i.e. they are special cases of the multiple testing problem

\[ H_0^i : \langle c_i, \theta \rangle = 0 \quad \text{vs.} \quad H_1^i : \langle c_i, \theta \rangle \neq 0, \quad i \in \{1, \ldots, r\} \]

where \( \theta \) is the vector aggregating the values of the parameter of interest at each factor level and \( c_1, \ldots, c_r \) are
contrast vectors of according dimension $[1, 5, 17]$. The matrix $C$ with columns $c_1, \ldots, c_p$ is the contrast matrix characterizing the multiple testing problem. As our focus is on factorial diagnostic trials with the partial AUC as the parameter of interest, we shall investigate the testing problem (1) for $\theta = \theta_{p,q}$.

Konietschke et al. [11] discussed this problem for the total AUC (i.e. $\theta = \theta_{1,0}$) and proposed a nonparametric multiple contrast test procedure to deal with it. They proved that the proposed test asymptotically controls the family-wise type I error rate. However, an application to the partial AUC, i.e. the general case $p,q \in [0,1]$ was beyond the scope of their results. In sections 3 and 4 we will close this gap. Based on a nonparametric estimator $\hat{\theta}_{p,q,n}$ of $\theta_{p,q}$, we will construct a family of tests $\{\theta_{i,n}: i = 1, \ldots, r\}$ designed to simultaneously test any selection of hypotheses $H_{i,n}^{1}, \ldots, H_{i,n}^{m}$, $1 \leq i_1 < \ldots < i_m \leq r$. Thereafter, we will present a general asymptotic theory of the involved estimator ensuring that our test family asymptotically controls the family-wise type I error rate in the strong sense.

3. A nonparametric estimator and multiple contrast test

In this section we will construct a family of tests $\{\theta_{i,n}: i \in \{1, \ldots, r\}\}$ for the above formulated multiple testing problem. Each test statistic will be based on a nonparametric estimator $\hat{\theta}_{p,q,n}$ of $\theta_{p,q}$, and the family will be constructed according to the well established multiple contrast test principle [4, 12]. The selection of the acceptance regions will be based on quantiles of the joint distribution of the involved test statistics, which we will approximate using the studentized empirical bootstrap. This approach often achieves higher order accuracy than just using the quantiles of the asymptotic distribution (see e.g. [2, 13]). Working with joint distributions ensures that we do not lose statistical information that may be carried by the structure of the dependencies between the individual test statistics. This promises to make the multiple contrast test approach more powerful than traditional methods based on p-value corrections, which tend to ignore such information [12]. Furthermore, it is a suitable basis for the construction of compatible simultaneous confidence intervals.

**Definition 3.** For $(a_n)_{n \in \mathbb{N}}, (b_n)_{n \in \mathbb{N}} \subset \mathbb{N}^+, i \in \{1, \ldots, k\}, u \in \mathbb{R}$, and $n \in \mathbb{N}$, let $F_{i,n}(u) = \frac{1}{a_n} \sum_{r=1}^{a_n} \mathbb{I}\{\xi_r(i) \leq u\}$ and $\hat{a}_{i,n} = F_{i,n}^{-1}(1-p)$. Analogously we define $G_{i,n}(u)$ and $\hat{b}_{i,n} = G_{i,n}^{-1}(1-q)$. The estimator $\hat{\theta}_{p,q,n}$ of $\theta_{p,q}$ is then

$$\hat{\theta}_{p,q,n} = \sum_{i=1}^{n} e_i \int_{[a_{i,n}, b_{i,n}]} (G_{i,n}(\hat{b}_{i,n}) - G_{i,n}(u)) \ dF_{i,n}(u).$$

Each component $\hat{\theta}_{p,q}(i)$ of $\hat{\theta}_{p,q}$ is a trimmed Mann–Whitney statistic. This can be seen as follows. Let for simplicity $k = 1$, and denote with $\eta_{(r)}$ and $\zeta_{(r)}$ the $r$th order statistics of the samples $\{\eta_{1,n}, \eta_{2,n}\}$ and $\{\xi_{1,n}, \xi_{2,n}\}$, respectively. Then

$$\int_{[a_{1,n}, b_{1,n}]} (G_{1,n}(\hat{b}_{1,n}) - G_{1,n}(u)) \ dF_{1,n}(u)$$

$$= \frac{1}{a_n} \sum_{r=1}^{a_n} \mathbb{I}\{\zeta_{(1-n(1-p))} < \xi_{(1-n(1-q))}\} \left[ \frac{1}{\beta_n} \sum_{s=1}^{\beta_n} \mathbb{I}\{\eta_{(s)} \leq \eta_{(1-n(1-q))}\} - \mathbb{I}\{\xi_{(r)} \leq \zeta_{(r)}\} \right]$$

$$= \frac{1}{a_n} \sum_{r=1}^{a_n} \sum_{s=1}^{\beta_n} \mathbb{I}\{\zeta_{(1-n(1-p))} < \eta_{(1-n(1-q))}\}$$

$$= \frac{1}{a_n} \sum_{r=1}^{a_n} \sum_{s=1}^{\beta_n} \mathbb{I}\{\eta_{(s)} < \eta_{(1)}\}.$$  

We see that setting $(p,q) = (1,0)$ results in the usual untrimmed Mann–Whitney estimator of $\theta_{1,0}$.

$$\hat{\theta}_{1,0,n} = \frac{1}{a_n \beta_n} \sum_{r=1}^{a_n} \sum_{s=1}^{\beta_n} \mathbb{I}\{\xi_{(r)} < \eta_{(s)}\}.$$
We define the matrix-valued statistic \( \hat{\Sigma}_n = (\partial_n(i,j))_{i,j=1}^{p+q} \) by

\[
\hat{\sigma}_n(i,j) = \frac{a_n + \beta_n}{\beta_n a_n} \sum_{s_1,s_2=1}^{s_n} \mathbb{I}\{a_i < \eta_{s_1(i)} \leq b_i\} \mathbb{I}\{a_j < \eta_{s_2(j)} \leq b_j\} \left[ \mathbb{E}_n(\hat{\xi}_{s_1(i)}(i), \hat{\xi}_{s_2(j)}(j)) - \mathbb{E}_n(\eta_{s_1(i)}(i), \eta_{s_2(j)}(j)) \right]
\]

\[
+ \frac{a_n + \beta_n}{\beta_n a_n} \sum_{r_1,r_2=1}^{a_n} \mathbb{I}\{a_i < \tilde{\xi}_{r_1(i)} \leq b_i\} \mathbb{I}\{a_j < \tilde{\xi}_{r_2(j)} \leq b_j\} \left[ \mathbb{G}_n(\hat{\xi}_{r_1(i)}(i), \hat{\xi}_{r_2(j)}(j)) - \mathbb{G}_n(\xi_{r_1(i)}(i), \xi_{r_2(j)}(j)) \right]
\]

It will turn out soon that \( \hat{\sigma}_{p,q,n} - \sigma_{p,q} \to 0 \) in probability. Hence, it seems sensible to test the hypothesis \( H_0: (c_{\delta}, \theta_{p,q}) = 0 \) by assessing the magnitude of \( (a_n + \beta_n)^{1/2}(c_{\delta}, \hat{\theta}_{p,q,n})/\left( \text{var}(c_{\delta}, \hat{\theta}_{p,q,n}) \right)^{1/2} \). Of course, \( \text{var}(c_{\delta}, \hat{\theta}_{p,q,n}) \) is unknown, but we will see that \( \sum_{x=1}^{\infty} \mathbb{E}_n(\eta_{s_1(i)}(i), \eta_{s_2(j)}(j)) \) is a consistent estimator of the asymptotic variance of \( (a_n + \beta_n)^{1/2}(c_{\delta}, \hat{\theta}_{p,q,n}) \).

**Definition 5.** The bootstrap samples \( \{\hat{\xi}_1^{(i)}, \ldots, \hat{\xi}_n^{(i)}\} \) and \( \{\eta_1^{(i)}, \ldots, \eta_{\beta_n}^{(i)}\} \) are drawn with replacement from the original samples \( \{\xi_1, \ldots, \xi_n\} \) and \( \{\eta_1, \ldots, \eta_{\beta_n}\} \), respectively, such that bootstrap and original samples are independent. If we apply Definitions 3 and 4 to the bootstrap samples instead of the original samples, we obtain the bootstrap versions of \( \hat{\theta}_{p,q,n} \) and \( \hat{\Sigma}_n \), to which we refer with \( \hat{\theta}_{p,q,n} \) and \( \hat{\Sigma}_n \), respectively.

At last we define the test family for our multiple testing problem. It is designed to keep the family-wise type I error rate asymptotically below a prescribed level \( \delta \in (0,1) \).

**Definition 6.** Let \( p,q \in (0,1) \) or \( (p,q) = (1,0) \), and let \( V_n \) and \( V_n^* \) be two diagonal matrices with \( \text{diag}(V_n) = \text{diag}(C^T \hat{\Sigma}_n C) \) and \( \text{diag}(V_n^*) = \text{diag}(C^T \hat{\Sigma}_n C) \). We define the test statistic \( T_n = (a_n + \beta_n)^{1/2} V_n^{-1/2} C^T \hat{\theta}_{p,q,n} \) and the bootstrap statistic \( \hat{S}_n = (a_n + \beta_n)^{1/2} (V_n^*)^{-1/2} (C^T \hat{\theta}_{p,q,n} - C^T \hat{\theta}_{p,q,n}) \). Let

\[
q(S_n^*:x) = \inf \left\{ t \geq 0 : \text{Pr}\{|S_n^*|_{t} \leq t | \xi_1, \ldots, \xi_n, \eta_1, \ldots, \eta_{\beta_n} \} \geq x \right\}
\]

denote the equi-coordinate quantile of \( S_n^* \). To test the hypothesis \( H_0 \), we use the decision function

\[
\varphi_{i,\delta}(\xi_1, \ldots, \xi_n, \eta_1, \ldots, \eta_{\beta_n}) = \begin{cases} 0 & \text{if } |T_n, e_i| \leq q(S_n^*:1-\delta) \\ 1 & \text{else.} \end{cases}
\]

We further define \( q_{i,\delta} = \max \{ \varphi_{i,\delta} : i \in \{1, \ldots, r\} \} \) and call it partial AUC maximum test if \( (p,q) \neq (0,1) \). Otherwise it is called total AUC maximum test.

4. **Theoretical main results**

**Definition 7.** For \( T \subset \mathbb{R} = \mathbb{R} \cup \{\pm \infty\} \), the space \( (\ell_\infty(T), d_\infty) \) is the set of all bounded functions \( g : T \to \mathbb{R} \), equipped with the uniform metric, \( d_\infty(g,h) := \sup_{t \in T} |g(t) - h(t)| \). Let \( (\ell_\infty(T), d_\infty) \) denote the 2-fold product space \( (\ell_\infty(T) \times \ldots \times \ell_\infty(T)) \) equipped with the metric

\[
d_\infty^{2x}(x_1, \ldots, x_{2n}, y_1, \ldots, y_{2n}) := \max_{i \in \{1, \ldots, 2n\}} d_\infty(x_i, y_i).
\]
Henceforth, $\ell^2_{\infty}$ shall denote $\ell^2_{\infty}(\mathbb{R})$. For any $n \in \mathbb{N}_+$, let $X_n$ be an $(\ell^2_{\infty},d^2_{\infty})$-valued random element defined by
\[
t \mapsto X_n(t) = \sum_{i=1}^{k} e_i a_n^{1/2} \left[ F_{i,n}(t) - F_i(t) \right] + e_{k+i} b_n^{1/2} \left( G_{i,n}(t) - G_i(t) \right).
\]

**Theorem 1.** Let $H(x_1, \ldots, x_k, y_1, \ldots, y_k) = F(x_1, \ldots, x_k)G(y_1, \ldots, y_k)$ be the cumulative distribution function of \((\xi_1(1), \ldots, \xi_k(\kappa), \eta_1(1), \ldots, \eta_k(1))\). Then, as $n \to \infty$, the sequence $\{X_n\}_{n \in \mathbb{N}}$ converges weakly in $(\ell^2_{\infty},d^2_{\infty})$ to a tight $(\mathcal{F} - \mathcal{B}(\ell^2_{\infty}))$-measurable centered gaussian random element $X_0 = (B_1, \ldots, B_{2\kappa})$ with covariance function
\[
\text{cov}(B_i(u), B_j(v)) = \begin{cases} 
F(k_{i,j}(u,v)) - F_i(u)F_j(v) & \text{if } s, t \in \mathbb{R}; i, j \in \{1, \ldots, \kappa\}, \\
G(k_{i,j}(u,v)) - G_i(u)G_j(v) & \text{if } s, t \in \mathbb{R}; i, j \in \{k+1, \ldots, 2\kappa\}, \\
H(k_{i,j}(u,v)) - F_i(u)G_j(v) & \text{if } s, t \in \mathbb{R}; i \in \{1, \ldots, \kappa\}, j \in \{k+1, \ldots, 2\kappa\}, 
\end{cases}
\]
where $k_{i,j}(s,t)$ denotes a vector of suitable dimension satisfying
\[
\langle k_{i,j}(u,v), e_k \rangle = \begin{cases} 
u & \text{if } k = i \neq j, \\
u & \text{if } k = j \neq i, \\
u \land v & \text{if } k = i = j, \\
\infty & \text{if } k \in \{i, j\}. 
\end{cases}
\]

**Definition 8.** Let $D(\mathbb{R})$ be the set of right continuous real functions with left limits, and $D$ the set of pairs \((\vartheta_1, \vartheta_2) \in D(\mathbb{R}) \times D(\mathbb{R})\) such that $\vartheta_1$ has variation bounded by 1. Furthermore, set $D_1 = D^{2\kappa}$, and $D_2 = D \times \mathbb{R}^2$. For any real function $\vartheta$, let $\|\vartheta\|_\infty = \sup_{x \in \text{Dom}(\vartheta)} |\vartheta(x)|$. We consider the norms $\| \cdot \|_{D_1}$ and $\| \cdot \|_{D_2}$ given by
\[
\| (\vartheta_1, \ldots, \vartheta_{2\kappa}) \|_{D_1} = \max_{i \in \{1, \ldots, 2\kappa\}} \| \vartheta_i \|_\infty, \\
\| (\vartheta_1, \vartheta_2, x_1, x_2) \|_{D_2} = \max \{ \| \vartheta_1 \|_\infty, \| \vartheta_2 \|_\infty, |x_1|, |x_2| \}.
\]
For $p, q \in (0, 1)$ and $i \in \{1, \ldots, \kappa\}$, we define maps $\psi^{(i)}_{p,q} : D_1 \to D_2$, $\phi_{p,q} : D_2 \to \mathbb{R}$, and $\tau_{p,q} : D_1 \to \mathbb{R}$ by
\[
\psi^{(i)}_{p,q}(\vartheta_1, \ldots, \vartheta_{2\kappa}) = (\vartheta_1, \vartheta_{k+i}, \vartheta_1^{-1}(1-p), \vartheta_{k+i}^{-1}(1-q)), \\
\phi_{p,q}(\vartheta, x_1, x_2) = \int (\vartheta(b) - \vartheta(u)) \ dB(u), \\
\tau_{p,q} = (\phi_{p,q} \circ \psi^{(1)}_{p,q}, \ldots, \phi_{p,q} \circ \psi^{(\kappa)}_{p,q})^T.
\]
The map $\tau_{1,0} : D_1 \to \mathbb{R}$ is defined by
\[
\tau_{1,0}(\vartheta_1, \ldots, \vartheta_{2\kappa}) = \sum_{i=1}^{\kappa} e_i \int_R \left( 1 - \vartheta_{k+i}(u) \right) \ dB(u).
\]

**Lemma 1.** For $p, q \in (0, 1)$, the function $\tau_{p,q} : (D_1, \| \cdot \|_{D_1}) \to (\mathbb{R}^\kappa, \| \cdot \|_\infty)$ is Hadamard differentiable at the point $(F_1, \ldots, F_k, G_1, \ldots, G_k) \in D_1$, tangentially to the set
\[
D_0 := \{(h_1, \ldots, h_{2\kappa}) \in D_1 : \text{for each } i \in \{1, \ldots, \kappa\}, h_i \text{ is continuous at } F_i^{-1}(1-p), h_{k+i} \text{ is continuous at } G_i^{-1}(1-q) \}.
\]
Its derivative at $(F_1, \ldots, F_k, G_1, \ldots, G_k)$ is
\[
D\tau_{p,q}(F_1, \ldots, F_k, G_1, \ldots, G_k)(h_1, \ldots, h_{2\kappa})
\]
sequences with Lipschitz constant at most \( \alpha \).

Let \( \text{Lemma 3.} \)

The corresponding covariance matrix \( \Sigma_{\theta, p, q} \) is distributed random vector. As a side result we obtain an explicit form of that limit,

Theorem 2. Suppose that \( \lim_{n \to \infty} a_n/(\alpha_n + \beta_n) = \lambda \in (0,1). \) Then, as \( n \to \infty \), the sequence of random vectors \( \{(\alpha_n + \beta_n)^{1/2}(\hat{\theta}_{p,q,n} - \theta_{p,q,n})\}_{n \in \mathbb{N}} \) converges weakly to the normally distributed random vector

The limit \( w_{p,q} \) has mean zero and the elements of its covariance matrix \( \Sigma_{p,q} \) are

Corollary 1. The statistic \( \hat{\alpha}_{p,q}(i,j) \) is a consistent estimator of \( \sigma_{p,q}(i,j) \).

Theorems 1 and 2 are valid without the assumption that \( \sigma(\xi_r : r \in \mathbb{N}_+) \) and \( \sigma(\eta_s : s \in \mathbb{N}_+) \) are independent. In this case, the covariance \( \sigma_{p,q}(i,j) \) has the additional addend

It is already well known that the sequence \( \{(\alpha_n + \beta_n)^{1/2}(\hat{\theta}_{p,q,n} - \theta_{p,q,n})\}_{n \in \mathbb{N}} \) converges weakly to a normally distributed random vector. As a side result we obtain an explicit form of that limit,

The corresponding covariance matrix \( \Sigma_{1,0} \) has the same form as \( \Sigma_{p,q} \) except that \( D = \mathbb{R}^2 \).

Lemma 2. Under the conditions of Theorem 2 the sequence \( \{(\alpha_n + \beta_n)^{1/2}(\hat{\theta}_{p,q,n} - \theta_{p,q,n})\}_{n \in \mathbb{N}} \) converges conditionally in distribution to \( w_{p,q} \), i.e.

\( \sup_{h \in \mathbb{R}^2} \left| \mathbb{E} \left[ h((\alpha_n + \beta_n)^{1/2}(\hat{\theta}_{p,q,n} - \theta_{p,q,n})) \right] \right| = 0 \)

in outer probability as \( n \to \infty \), where \( \mathbb{R}^2 \) denotes the set of bounded Lipschitz functions \( \mathbb{R}^2 \to [-1,1] \) with Lipschitz constant at most 1.

Based on the Glivenko–Cantelli Theorem for Efron's Bootstrap [26, Theorem 3.2], we can additionally infer that the bootstrap version of the covariance estimator is consistent.

Lemma 3. Let \( \hat{\theta}_{p,q,n}(i,j) \) denote the bootstrap version of \( \hat{\alpha}_{p,q,n}(i,j) \). Then, for almost all data generating sequences \( \{\xi_n\}_{n \in \mathbb{N}}, \{\eta_n\}_{n \in \mathbb{N}} \) and every \( \epsilon > 0 \),

\( \Pr \left[ |\hat{\theta}_{p,q,n}(i,j) - \hat{\alpha}_{p,q,n}(i,j)| > \epsilon \mid \xi_1, \ldots, \xi_n, \eta_1, \ldots, \eta_n \right] \to 0 \),

as \( n \to \infty \)
Theorem 3. Let $p, q \in (0,1)$ or $(p, q) = (1,0)$. Then, under the conditions of Theorem 2, the family of tests \{\varphi_{i,i}: i \in \{1,\ldots,r\}\} for the testing problem (1) asymptotically controls the family wise error rate in the strong sense; i.e. for any subset $\{i_1,\ldots,i_m\} \subset \{1,\ldots,r\}$, if $H_0^{i_1} \land \cdots \land H_0^{i_m}$ is true, then

$$\lim_{n \to \infty} \Pr\left(\bigcap_{j=1}^m \{\varphi_{i_j,\delta}(\xi_1,\ldots,\xi_{\alpha},\eta_1,\ldots,\eta_{\beta}) = 1\}\right) \leq \delta.$$ 

The test $\varphi_\delta$ for the global hypotheses $H_0: C^T \theta_{p,q} = 0$ vs. $H_1: C^T \theta_{p,q} \neq 0$ is asymptotically of size $\delta$.

5. Computer experiments

5.1. Material and methods

To illustrate and corroborate our theoretical findings, we conducted a series of computer experiments, focusing on the behaviour of the maximum test $\varphi_\delta$ with $\delta = 0.05$ in a balanced diagnostic trial (i.e. $\alpha = \beta$) with one-way layout and three factor levels. We investigated type I error rates to corroborate the result of Theorem 3 and thereby implicitly also Theorem 2 and Lemma 2. Additionally we conducted power simulations to compare the efficiencies of the total and partial AUC maximum tests. In all instances we approximated the bootstrap quantiles based on 2000 independent repetitions. After 10,000 simulation runs we computed the average errors. All simulations were carried out using the R programming language, version 4.1.0 [21]. The code is available from the authors upon request.

Type I error simulations. We set $\kappa = 3$ and defined the joint distribution function of the observations by $F(u_1,\ldots,u_6) = \mathcal{C}(F_1(u_1),F_2(u_2),F_3(u_3),G_1(u_4),G_2(u_5),G_3(u_6))$, where $\mathcal{C}$ is a Gaussian copula with a Spearman correlation matrix

$$R_\alpha = \begin{pmatrix}
1.00 & 0.79 & 0.38 & 0.00 & 0.00 & 0.00 \\
0.79 & 1.00 & 0.79 & 0.00 & 0.00 & 0.00 \\
0.38 & 0.79 & 1.00 & 0.00 & 0.00 & 0.00 \\
0.00 & 0.00 & 0.00 & 1.00 & 0.79 & 0.38 \\
0.00 & 0.00 & 0.00 & 0.79 & 1.00 & 0.79 \\
0.00 & 0.00 & 0.00 & 0.38 & 0.79 & 1.00
\end{pmatrix}.$$ 

We chose $F_1, G_1, F_2, G_2, F_3, G_3$ as the cumulative distribution functions of $\mathcal{N}(0,1)$, $\mathcal{N}(0.5,1)$, $\exp(\mathcal{N}(0,1))$, $\exp(\mathcal{N}(0.5,1))$, $[1 + \exp(-\mathcal{N}(0,1))]^{-1}$, $[1 + \exp(-\mathcal{N}(0.5,1))]^{-1}$, respectively. We tested the global hypothesis $H_0: C^T \theta_{p,q} = 0$ for a $3 \times 3$ Tukey-type all pair comparison contrast matrix, i.e. the contrast vectors are $c_1 = (1,-1,0)^T$, $c_2 = (0,1,-1)^T$, and $c_3 = (1,0,-1)^T$. The type I error rates of $\varphi_\delta$ were computed for different pairs $(p,q) \in \{0,0.2,\ldots,1\} \times \{0,0.2,\ldots,1\}$ and are displayed in Table 1.

Power analysis. We conducted a power comparison of the total and the partial area under the curve multiple contrast test in the same setting as above. More specifically, we compared the power of $\varphi_\delta$ for testing $H_0: C^T \theta_{p,q}$ for $(p, q) = (0.6,0.4)$, $(p, q) = (0.8,0.6)$, and $(p, q) = (1,0)$. To that end, we had to chose the underlying distributional parameters such that the effect sizes $\|C^T \theta_{p,q}\|$ were approximately equal in all three settings. We achieved this by leaving $F_1, F_2, G_1, G_2, G_3$ as above and tuning the mean of $F_3$ such that we attained the desired effect size. Knowing the underlying distributions, we can numerically compute the corresponding partial area under the curve using deterministic numerical integration algorithms. Easing the computation are the facts that the partial AUC is invariant under monotone transformations and that the marginals $F_1,\ldots,G_3$ are mere monotone transformations of normal distributions. The results of the power comparisons are displayed in Table 2.
5.2. Results

Our type I error simulations demonstrate that $\phi_\delta$ rapidly attains the desired size of 0.05. However, the necessary sample size for this observation varied significantly between the different settings. In some cases the test is rather conservative for small sample sizes, e.g. $n = 30$. With $n = 80$ observations per group, the test had type I error rates close to the desired level for most choices of $p$ and $q$.

As to the power simulations, the type II error rates were also quite sensitive to the choice of $p$ and $q$. In any case, we observe that the considered partial AUC maximum tests detected the deviances from the global null hypothesis more frequently than the total AUC test, at least for sample sizes sufficiently large for the tests to attain their nominal sizes as indicated by Table 1.

| $(p, q)$ | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---------|----|----|----|----|----|----|----|-----|
| (0.2, 0.0) | 0.0088 | 0.0180 | 0.0254 | 0.0307 | 0.0345 | 0.0379 | 0.0388 | 0.0393 | 0.0414 | 0.0461 | 0.0430 |
| (0.4, 0.0) | 0.0272 | 0.0378 | 0.0414 | 0.0410 | 0.0404 | 0.0441 | 0.0488 | 0.0443 | 0.0499 | 0.0477 | 0.0469 |
| (0.4, 0.2) | 0.0119 | 0.0207 | 0.0309 | 0.0376 | 0.0409 | 0.0403 | 0.0448 | 0.0428 | 0.0476 | 0.0466 | 0.0451 |
| (0.6, 0.0) | 0.0400 | 0.0428 | 0.0435 | 0.0441 | 0.0502 | 0.0478 | 0.0465 | 0.0435 | 0.0454 | 0.0441 | 0.0504 |
| (0.6, 0.2) | 0.0308 | 0.0215 | 0.0327 | 0.0310 | 0.0376 | 0.0418 | 0.0420 | 0.0480 | 0.0422 | 0.0427 | 0.0486 |
| (0.6, 0.4) | 0.0140 | 0.0222 | 0.0273 | 0.0354 | 0.0416 | 0.0434 | 0.0440 | 0.0465 | 0.0454 | 0.0458 | 0.0468 |
| (0.6, 0.6) | 0.0168 | 0.0200 | 0.0340 | 0.0334 | 0.0372 | 0.0492 | 0.0416 | 0.0401 | 0.0442 | 0.0463 | 0.0508 |
| (0.8, 0.0) | 0.0392 | 0.0443 | 0.0448 | 0.0467 | 0.0484 | 0.0472 | 0.0482 | 0.0526 | 0.0501 | 0.0459 | 0.0476 |
| (0.8, 0.2) | 0.0397 | 0.0436 | 0.0501 | 0.0482 | 0.0482 | 0.0485 | 0.0478 | 0.0536 | 0.0510 | 0.0511 | 0.0507 |
| (0.8, 0.4) | 0.0406 | 0.0431 | 0.0479 | 0.0508 | 0.0465 | 0.0505 | 0.0475 | 0.0501 | 0.0518 | 0.0480 | 0.0502 |
| (0.8, 0.6) | 0.0442 | 0.0420 | 0.0471 | 0.0496 | 0.0503 | 0.0519 | 0.0460 | 0.0498 | 0.0486 | 0.0487 | 0.0490 |
| (0.8, 0.8) | 0.0435 | 0.0463 | 0.0484 | 0.0480 | 0.0478 | 0.0508 | 0.0477 | 0.0484 | 0.0509 | 0.0507 | 0.0498 |
| (1.0, 0.0) | 0.0409 | 0.0457 | 0.0447 | 0.0470 | 0.0498 | 0.0553 | 0.0461 | 0.0503 | 0.0514 | 0.0536 | 0.0461 |
| (1.0, 0.2) | 0.0431 | 0.0486 | 0.0487 | 0.0482 | 0.0469 | 0.0505 | 0.0506 | 0.0504 | 0.0479 | 0.0459 | 0.0467 |
| (1.0, 0.4) | 0.0377 | 0.0437 | 0.0458 | 0.0433 | 0.0462 | 0.0459 | 0.0493 | 0.0497 | 0.0493 | 0.0463 | 0.0520 |
| (1.0, 0.6) | 0.0323 | 0.0413 | 0.0417 | 0.0448 | 0.0460 | 0.0458 | 0.0491 | 0.0469 | 0.0479 | 0.0544 | 0.0494 |
| (1.0, 0.8) | 0.0079 | 0.0180 | 0.0219 | 0.0292 | 0.0336 | 0.0388 | 0.0382 | 0.0412 | 0.0466 | 0.0391 | 0.0483 |

Table 1: Type I error rates for the partial AUC maximum test with Tukey-type contrast matrix.

| $(p, q)$ | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---------|----|----|----|----|----|----|----|-----|
| (0.6, 0.4) | 0.4910 | 0.7447 | 0.8713 | 0.9410 | 0.9743 | 0.9878 | 0.9967 | 0.9998 |
| (0.8, 0.6) | 0.6297 | 0.8504 | 0.9472 | 0.9835 | 0.9953 | 0.9986 | 0.9995 | 0.9999 |
| (1.0, 0.0) | 0.4397 | 0.5985 | 0.7420 | 0.8314 | 0.9111 | 0.9472 | 0.9695 | 0.9843 |
| (0.6, 0.4) | 0.1416 | 0.2572 | 0.3659 | 0.4669 | 0.5647 | 0.6465 | 0.7040 | 0.7549 |
| (0.8, 0.6) | 0.1858 | 0.3352 | 0.4736 | 0.6038 | 0.6846 | 0.7745 | 0.8287 | 0.8768 |
| (1.0, 0.0) | 0.1633 | 0.2111 | 0.2714 | 0.3387 | 0.3871 | 0.4454 | 0.4969 | 0.5528 |
| (0.6, 0.4) | 0.0285 | 0.0427 | 0.0697 | 0.0824 | 0.0901 | 0.1035 | 0.1170 | 0.1283 |
| (0.8, 0.6) | 0.0322 | 0.0493 | 0.0730 | 0.0913 | 0.1132 | 0.1273 | 0.1449 | 0.1639 |
| (1.0, 0.0) | 0.0548 | 0.0651 | 0.0683 | 0.0769 | 0.0811 | 0.0878 | 0.0934 | 0.0976 |

Table 2: Empirical power of the maximum test with Tukey-type contrast matrix for different effect sizes and values of $(p, q)$. 10
6. Discussion

6.1. Efficiency

The computer experiments seemed to corroborate our intuitive conjecture that partial AUC maximum tests are more efficient than their total AUC counterpart. We argue that these experimental findings are not mere coincidences. To this end, let us investigate the differences of the asymptotic covariance matrices $\Sigma_{p,q}$ and $\Sigma_{0,1}$ of $\hat{\theta}_{p,q,n}$ ($p, q \neq (0,1)$) and $\hat{\theta}_{0,1,n}$, respectively. If $\Delta = \Sigma_{0,1} - \Sigma_{p,q}$ is positive definite, Weyl’s inequality (see e.g. [22, Corollary 4.9]) implies that $\Sigma_{0,1}$ has larger eigenvalues than $\Sigma_{p,q}$, further implying that the partial AUC maximum test is asymptotically more efficient relatively to the total AUC maximum test, in the sense that infinitesimal deviances from the null are easier to detect for the former than for the latter. Since the overall picture is quite complex, we restrict the discussion to two special cases.

First, consider the case that $P_{0} = P_{1} \circ \ldots \circ P_{N}$ and $P_{(1)} = P_{1} \circ \ldots \circ P_{N}^{(1)}$, i.e. all components of $\theta_{0,1}$ and $\theta_{p,q}$ are estimated on the basis of mutually independent samples. Analogously to the proof of Theorem 2, we see that

$$\Delta(i,i) = \int_{\mathbb{R}^{2}(\alpha_{i},\beta_{i})} E[B_{i}(u)B_{i}(v)] P_{(1)}^{(2)}(dv, du)$$

$$+ \int_{\mathbb{R}^{2}(\alpha_{i},\beta_{i})} E[B_{i}(u)B_{i}(v)] P_{(1)}^{(0)}(dv, du) \geq 0,$$

since $E[B_{i}(u)B_{i}(v)] = F_{i}(u \wedge v) - F_{i}(u)F_{i}(v) \geq 0$ and $E[B_{i}(u)B_{i}(v)] = G_{i}(u \wedge v) - G_{i}(u)G_{i}(v) \geq 0$ for every $u, v \in \mathbb{R}$ and $r \in \{1, \ldots, k\}$. Hence, in this case $\Delta = \Sigma_{0,1} - \Sigma_{p,q}$ is a positive semidefinite diagonal matrix.

The second special case refers to the situation that $k = 2$, which corresponds to a comparison of two markers. Here we do not make any additional independence assumption. In this case $\Delta = \Sigma_{0,1} - \Sigma_{p,q}$ is a symmetric $\mathbb{R}^{2 \times 2}$ matrix with the same diagonal elements as in the previous case and off-diagonal value

$$\Delta(1,2) = \int_{\{\alpha_{1},\alpha_{2}\} \times \{\beta_{1},\beta_{2}\}} E[B_{1}(u)B_{2}(v)] P_{1}^{(1)} P_{2}^{(1)}(dv, du)$$

$$+ \int_{\{\alpha_{1},\alpha_{2}\} \times \{\beta_{1},\beta_{2}\}} E[B_{1}(u)B_{2}(v)] P_{1}^{(0)} P_{2}^{(0)}(dv, du).$$

The eigenvalues $\lambda_{1} \geq \lambda_{2}$ of $\Delta$ are the roots of $p(\lambda) = (\lambda - \Delta(1,1))((\lambda - \Delta(2,2)) - (\Delta(1,2))^{2}$. The first eigenvalue, $\lambda_{1}$, is always positive. The second eigenvalue, $\lambda_{2}$, is non-negative if and only if $|\Delta(1,2)|^{2} \leq \Delta(1,1)\Delta(2,2)$. Hence, the matrix is either positive semidefinite or indefinite, depending on the cross covariances of $(B_{1},B_{2},B_{3},B_{4})$. However, it is never negative definite.

In conclusion, inference for the partial AUC appears to be advantageous if no strong dependencies between $\sigma[\eta_{1}(s) : s \in \mathbb{N}]$ and $\sigma[\eta_{2}(s) : s \in \mathbb{N}]$ or between $\sigma[\xi_{1}(r) : r \in \mathbb{N}]$ and $\sigma[\xi_{2}(r) : r \in \mathbb{N}]$ are manifest. In the absence of such dependencies, the clinically relevant segments of the ROC curves are rather uninformative about the clinically relevant cases, leading to a positive definite matrix $\Delta$. Comparing two diagnostic markers based on partial areas under their respective ROC curves is then more efficient that comparing the total areas. The presence of strong inter-dependencies, on the other hand, opens the theoretical possibility that the clinically irrelevant region of the ROC curve of one marker carries information about the clinically relevant segment of the curve of another marker. In this case, $\Delta$ may be indefinite and the picture is somewhat unclear.

6.2. Quality of the bootstrap approximation

The ability of the bootstrap to approximate our test statistic’s distribution, and therefore the reliability of our inference method, hinges on the proximity of the test statistic to its weak limit [3]. Our numerical experiments suggest that this proximity varies between different settings. We want to provide some heuristic insights as to how the involved distributions $P_{0}$ and $P_{(1)}$ and the choice of $p$ and $q$ affect the test statistic’s asymptotic behavior. Suppose for the sake of simplicity that $\kappa = 1$ and $\alpha_{n} = \beta_{n} = n/2$. The derivative $Dr(F,G)$ is a linear
approximation of the functional $\tau$ around $(F,G)$. Hence,
\[
\begin{align*}
&n^{1/2} \left[ \tau(E_n, C_n) - \tau(F,G) \right] = D \tau(F,G) \bigg| n^{1/2} \left[ (E_n, C_n) - (F,G) \right]
\leq n^{1/2} \int_{(a,b)} (E_n(u_j) - F(u_j)) \, dG(u) - n^{1/2} \int_{(a,b)} (G_n(v_j) - G(v_j)) \, dF(u)
\approx \sum_{j=1}^N P(1) \left[ (u_{j-1}, u_j) \right] n^{1/2} \left[ E_n(u_j) - F(u_j) \right] - \sum_{j=1}^N P(0) \left[ (v_{j-1}, v_j) \right] n^{1/2} \left[ G_n(v_j) - G(v_j) \right]
= S_{1,n} + S_{2,n},
\end{align*}
\]
where $a = u_0 < \ldots < u_N = b$ and $a = v_0 < \ldots < v_N = b$ are sufficiently fine partitions and $N$ is sufficiently large. By the Lindeberg–Feller theorem and Slutsky's lemma, $S_{1,n}$ and $S_{2,n}$ converge weakly to two mutually independent normally distributed random variables. We invoke the Edgeworth expansion to assess the quality of this normal approximation. Let $\vartheta_j = F(u_j -)$, and denote with $\tilde{F}_j$ the cumulative distribution function of $n^{-1/2} \sum_{r=1}^n \{ 1 \{ \vartheta_r < u_j \} - \vartheta_j \} / (\vartheta_j (1 - \vartheta_j))^{1/2}$. Then
\[
\begin{align*}
\tilde{F}_j(x) &= \Phi(x) + \frac{1 - 2\theta_j}{2\pi \vartheta_j (1 - \vartheta_j)^{1/2}} \left( 1 - x^2 \right) \exp \left( -x^2/2 \right) n^{-1/2} + o(n^{-1/2}),
\end{align*}
\]
as $n \to \infty$ [3, p. 363]. Of course, the rate $O(n^{-1/2})$ with which $\tilde{F}_j(x)$ converges to $\Phi(x)$ is not affected by the involved model parameters. However, the constant terms in the second addend of the Edgeworth expansion [3] is sensitive to the shape of the distributions $P^{(0)}$, $P^{(1)}$ as well as the choice of $p$ and $q$. A problematic constellation with practical relevance is given by a pair of marker distributions $P^{(0)}$, $P^{(1)}$ that are well separated in combination with a choice $p < \epsilon$ and $q > 1 - \epsilon$ for small $\epsilon > 0$. This would result in an interval $(a, b]$ of vanishingly small length such that $S_{1,n}$ comprises only addends with $\vartheta_j$ close to 1, strongly inflating the constant in equation (3). Whereas this does not change anything on the asymptotic behavior of our test family $(\rho_{t,\delta})$, it will have a negative impact on its finite sample properties. Heuristically, this phenomenon is plausible if we recall the estimator’s property to be a trimmed Mann–Whitney statistic as displayed in line (2). Extreme values of $p$ and $q$ in combination with a small overlap between $P^{(0)}$ and $P^{(1)}$ can severely decrease the number of non-zero addends in (2), reducing the effective sample size.

6.3. Conclusion

In our view, multiple contrast tests for families of linear hypotheses about partial AUCs are a viable inference method for factorial diagnostic studies. We have demonstrated that they perform well for moderate sample sizes and found theoretical as well as empirical indications that it is more efficient to test linear hypotheses about the partial AUC rather than the total AUC. Hence, we believe that the partial area under the ROC curves should be considered more often as parameters of interest in factorial diagnostic studies. However, our discussion showed that the finite sample properties of our proposed inference methods for the partial AUC can be sensitive to the choices of clinically acceptable TPR and FPR. Especially when prior knowledge leads us to conjecture that the considered biomarkers have a very high discriminatory power, we should not define a too narrow clinically acceptable region.

7. Proofs

For $t \in \mathbb{R}^{2k}$ let $\pi_t : (\ell^2_{\infty}, d^2_{\infty}) \to \mathbb{R}$ be the coordinate projection $\pi_t(x) = x(t)$. With $\mathcal{D}^{2k}$ we denote the projection $\sigma$-field or cylindrical $\sigma$-field on $(\ell^2_{\infty}, d^2_{\infty})$, i.e. the $\sigma$-field generated by the coordinate projections. In the following, the symbol $\rightsquigarrow$ denotes weak convergence.

Proof of Theorem 7. We extend the result of Theorem 4 of the supplemental material, combining the ideas of van der Vaart and Wellner [24, p. 42] and Pollard [18, p. 97]. Essentially we use the continuous mapping theorem twice.
First, the map \( \varphi: (\ell^2\infty((0,1)), d_2^{\infty}) \to (\ell^\infty((0,2\kappa)), d_\infty) \),
\[ \varphi(x_1, \ldots, x_2k)(t) = \sum_{i=1}^{2k} x_i(t-i+1) I_{[i-1, i)}(t), \quad t \in [0, 2\kappa), \]
is an isometry. Hence, both \( \varphi \) and \( \varphi^{-1} \) are continuous, and with the continuous mapping theorem \cite[Theorem 1.3.6]{24} we conclude that \( \varphi(x_{1,n}, \ldots, x_{2k,n}) \to \varphi(x_{1,0}, \ldots, x_{2k,0}) \) in \( \ell^\infty((0,2\kappa)) \) if and only if \( (x_{1,n}, \ldots, x_{2k,n}) \to (x_{1,0}, \ldots, x_{2k,0}) \) in \( \ell^2\infty((0,1)), d^{\infty}_2 \).

Now consider \( U_n = (U_{1,n}, \ldots, U_{2k,n}) \in (\ell^2\infty((0,1)), d^{2\infty}_2) \),
\[ U_{i,n}(t) = n^{-1/2} \sum_{r=1}^{n} \left( I_{[r/n, r/n+t]} - \tilde{G}(t) \right), \quad i, \kappa \in [1, \ldots, 2\kappa), \]
where \( \tilde{G} \) denotes the cumulative distribution function of a Uniform[0,1] distribution. For all \( i \in [1, \ldots, 2\kappa) \), Donsker’s Theorem \cite[p. 96]{13} implies that \( U_{i,n} \to U_i \) in \( \ell^\infty((0,1), d_\infty) \), where \( U_i \) is a \( \tilde{G} \)-Brownian bridge.

By Prohorov’s Theorem \cite[Thm 1.3.9]{24} in combination with Lemmas 1.4.3 and 1.4.4 of \cite{24}, we conclude that there exists a subsequence \( (U_{n_i}) \) that converges weakly to a tight Borel measurable random element \( U_0 \in (\ell^2\infty((0,1)), d^{2\infty}_2) \). Suppose there is another such subsequence \( (U_{n_i}) \) with corresponding weak limit \( V_0 \). As noted before, \( \varphi(U_{n_i}) \to \varphi(U_0) \) and \( \varphi(U_{n_i}) \to \varphi(V_0) \). Both limits are Borel measurable tight random elements. We will show that \( \varphi(U_0) \) and \( \varphi(V_0) \) have the same distribution. For any \( k \in \mathbb{N} \), the mapping \( x \to (\pi_1 x, \ldots, \pi_{2k} x): (\ell^\infty((0,2\kappa)), d_\infty) \to \mathbb{R}^k \) is continuous. By the continuous mapping theorem, \( \{\pi_1 \varphi(U_{n_i}), \ldots, \pi_{2k} \varphi(U_{n_i})\} \to \{\pi_1 \varphi(U_0), \ldots, \pi_{2k} \varphi(U_0)\} \) as well as \( \{\pi_1 \varphi(U_{n_i}), \ldots, \pi_{2k} \varphi(U_{n_i})\} \to \{\pi_1 \varphi(V_0), \ldots, \pi_{2k} \varphi(V_0)\} \). But the multivariate Lindeberg-Feller Theorem, both limit distributions coincide. Since tight Borel probability measures on \( (\ell^\infty, \mathcal{B}(\ell^\infty)) \) are uniquely defined by their finite dimensional marginals \cite[Lemma 1.5.3]{24}, we conclude that \( \varphi(U_0) \) and \( \varphi(V_0) \) have the same distribution. Since all subsequences of \( \varphi(U_{n_i}) \) converge to the same weak limit \( \varphi(U_0) \) it follows that \( \varphi(U_n) \to \varphi(U_0) \), which implies \( U_n \to U_0 \). Note that \( \varphi(U_0) \) is a centered Gaussian process and so is \( U_0 \).

With \( F_i(-\infty) = 0 \) and \( F_i(\infty) = 1 \), we can view each \( F_i \) as an element in \( (\ell^\infty, d_\infty) \). We define the map \( \hat{H}: (\ell^2\infty((0,1)), d^{\infty}_2) \to (\ell^\infty((0,2\kappa)), d^\infty_\infty) \) by \( \hat{H}(x_1, \ldots, x_{2k}) := \{x_1(F_1(t)), \ldots, x_{2k}(G_k(t))\} \). Observe that \( d^{2\infty}_\infty(\hat{H}(x), \hat{H}(y)) \leq d^{2\infty}_\infty(x, y) \) for all \( x, y \in (\ell^2\infty((0,1)), d^{\infty}_2) \), which makes \( \hat{H} \) continuous. Therefore,
\[ n^{-1/2} \sum_{r=1}^{n} \left( I_{[\varphi_i^{-1}[0, r/n], \varphi_i^{-1}[0, r/n+t]} - \tilde{G}(t) \right), \ldots, n^{-1/2} \sum_{r=1}^{n} \left( I_{[\varphi_{2k}^{-1}[0, r/n], \varphi_{2k}^{-1}[0, r/n+t]} - \tilde{G}(t) \right) = \hat{H}(U_n) \to \hat{H}(U_0). \]

However, for any \( i \in [1, \ldots, k) \), \( F_i \) and \( G_i \) are the cumulative distribution functions of \( F_i^{-1}(t_i, r) \) and \( G_i^{-1}(t_i, r) \), respectively, which means that \( \hat{H}(U_n) \) and \( X_n \) have the same distribution on \( (\ell^\infty, \mathcal{B}(\ell^\infty)) \). With Lemma \[\text{from the supplemental material} \] we conclude that \( X_n \to \hat{H}(U_0) \) as well. From the definition of \( \hat{H} \), it follows that \( \hat{H}(U_0) \) is a centered Gaussian process.

In a last step, we compute the corresponding covariance function. We start with the covariance of \( U_0 = (U_{1,0}, \ldots, U_{2k,0}) \).
\[ \text{cov}(U_{i,0}(s), U_{j,0}(t)) = \text{cov}(U_{i,0,0}(s), U_{j,0,0}(t)) = |s|^k \left( 1 - |s|^k \right) \delta(s, t) - \tilde{G}(s) \tilde{G}(t), \]
\[ \text{cov}(\tilde{H}(U_0)) \text{, } (\hat{H}(U_0))_j(t) = \text{cov}(U_{i,0}(F_i(s)), U_{j,0}(F_j(t))) \]
For the cases $i, j \in \{\kappa + 1, \ldots, 2\kappa\}$ as well as $i \in \{1, \ldots, \kappa\}$, $j \in \{1, \ldots, 2\kappa\}$, the argument is completely analogous. 

**Proof of Lemma 2** First we show that $\psi_{p,q}$ is Hadamard differentiable at $(F_1, \ldots, F_{\kappa}, G_1, \ldots, G_{\kappa})$ tangentially to $D_0$, with derivative

$$D\psi_{p,q}(F_1, \ldots, F_{\kappa}, G_1, \ldots, G_{\kappa})[h_1, \ldots, h_{2\kappa}] = \left( \frac{h_i(F_{i-1}(1-p) - F_i^{-1}(1-p))}{f_i(F_i^{-1}(1-p))}, \frac{h_{\kappa+i}(G_{i-1}(1-q))}{g_i(G_i^{-1}(1-q))} \right).$$

Let the sequences $(t_r)_{r \in \mathbb{N}} \subset \mathbb{R}$ and $(h_{1,r}, \ldots, h_{2\kappa,r})_{r \in \mathbb{N}} \subset D_1$ be chosen such that $t_r \to 0$ and $\|(h_{1,r}, \ldots, h_{2\kappa,r}) - (h_1, \ldots, h_{2\kappa})\|_{D_1} \to 0$ as $r \to \infty$. Note that

$$\frac{1}{t_r} \left( \psi_{p,q}(F_1 + t_r h_{1,r}, \ldots, F_{\kappa} + t_r h_{2\kappa,r}) - \psi_{p,q}(F_1, \ldots, F_{\kappa}) \right) = \left( h_{i,r} h_{i+\kappa,r}, \frac{(F_i + t_r h_{i+\kappa,r})^{-1}(1-q) - F_i^{-1}(1-q) - (G_i + t_r h_{\kappa+i,r})^{-1}(1-p) + G_i^{-1}(1-p)}{t_r} \right).$$

This converges in $\|\cdot\|_2$ to the prescribed limit (consult Lemma 21.3 in [23] for the Hadamard derivative of the quantile transform).

In a second step, we have to show that $\phi_{p,q}$ is Hadamard differentiable at each $(F_1, G_1)$, tangentially to $D\phi_{p,q}(F_1, G_1)[D_0]$, with derivative

$$D\phi_{p,q}(F_1, G_1)[h_i, h_{\kappa+i}, x, y] = \left[ y g_i(b) (F_i(b) - F_i(a)) - xf_i(a) (G_i(b) - G_i(a)) \right]$$

$$+ \int_{[a,b]} \left( h_{\kappa+i}(b) - h_{\kappa+i}(u) \right) dF_i(u) + \int_{[a,b]} \left( h_i(u) - h_i(a) \right) dG_i(u)$$

$$= \int_{[a,b]} \left( h_{\kappa+i}(b) - h_{\kappa+i}(u) + y g_i(b) \right) dF_i(u) + \int_{[a,b]} \left( h_i(u) - h_i(a) - xf_i(a) \right) dG_i(u)$$

To that end, let $(h_{1,r}, h_{\kappa+1,r}, x, y)_{r \in \mathbb{N}}$ be a sequence such that $\|(h_{1,r}, h_{\kappa+1,r}, x, y) - (h_1, h_{\kappa+1}, x, y)\|_{D_2} \to 0$, as $r \to \infty$, and $(F_1 + t_r h_{1,r}, G_1 + t_r h_{\kappa+1,r}, a + t_r x, b + t_r y) \in D_2$ for all $r$. Then

$$\frac{1}{t_r} \left[ \phi_{p,q}(F_1 + t_r h_{1,r}, G_1 + t_r h_{\kappa+1,r}, a + t_r x, b + t_r y) - \phi_{p,q}(F_1, G_1)[a, b] \right]$$

$$= \frac{1}{t_r} \left[ \phi_{p,q}(F_1 + t_r h_{1,r}, G_1 + t_r h_{\kappa+1,r}, a + t_r x, b + t_r y) - \phi_{p,q}(F_1, G_1)[a, b] \right]$$

$$- \frac{1}{t_r} \left[ \phi_{p,q}(F_1 + t_r h_{1,r}, G_1 + t_r h_{\kappa+1,r}, a, b) \right]$$

$$+ \frac{1}{t_r} \left[ \phi_{p,q}(F_1 + t_r h_{1,r}, G_1 + t_r h_{\kappa+1,r}, a, b) - \phi_{p,q}(F_1, G_1)[a, b] \right]$$

$$= D_{i,r}^{(1)} + D_{i,r}^{(2)}.$$
According to the chain rule for Hadamard differentiation [24, Lemma 3.9.6],

\[
D[\psi_{p,q}] (F_1, \ldots, G_k)[h_1, \ldots, h_2]
= D\psi_{p,q} \left[ \frac{D\psi_{p,q}}{D\psi_{p,q}}(F_1, \ldots, G_k) \right] [D\psi_{p,q}(F_1, \ldots, G_k)[h_1, \ldots, h_2]]
= \int_{F^{-1}(1-p)G^{-1}(1-q)} h_1(u) \ dG_i(u) - \int_{F^{-1}(1-p)G^{-1}(1-q)} h_{k+i}(u) \ dF_i(u).
\]

This implies the first assertion.

As to the derivative of \( r_{1,0} \), note that we do not have to apply the chain rule and that the term \( D^{(1)}_{i,k} \) disappears in this case. The analysis of \( D^{(2)}_{i,k} \) is very similar to the case of \( r_{p,q} \).

**Proof of Theorem 2.** The weak convergence to \( w_{p,q} \) follows from the functional delta method [24, Theorem 3.9.4]. As linear functionals of Gaussian processes, the limits are Gaussian, i.e. multivariate normal [24, Lemma 3.9.8]. The covariance \( \text{cov}(\langle w_{p,q}, e_i \rangle, \langle w_{p,q}, e_j \rangle) \) is a sum of four covariances,

\[
\text{cov} \left( \int_{[a_i,b_i]} \lambda^{-1/2} B_j(u) \ dG_i(u) - \int_{[a_i,b_i]} (1 - \lambda)^{-1/2} B_{k+i}(u) \ dF_i(u), \right.
\]

\[
\left. \int_{[a_j,b_j]} \lambda^{-1/2} B_j(u) \ dG_j(u) - \int_{[a_j,b_j]} (1 - \lambda)^{-1/2} B_{k+j}(u) \ dF_j(u) \right).
\]

Using the fact that the brownian bridge has continuous sample paths and that \( EB_i(u) = 0 \) for any \( u \in \mathbb{R} \), we can apply Fubini's theorem to conclude that

\[
T_1 = \int_{[a_i,b_i]} \int_{[a_j,b_j]} \lambda^{-1} E [B_i(u)B_j(v)] P_j(1)(dv)P_i(1)(du) = \lambda^{-1} \int_D \text{cov}(B_i(u), B_j(v)) P_i(1) \otimes P_j(1)(du, dv).
\]

The other three terms are computed analogously.

The proof that \( \sigma_{p,q,n}(i,j) \to \sigma_{p,q}(i,j) \) almost surely as \( n \to \infty \) is entirely based on the Gliwenko–Cantelli theorem. We provide it in the supplemental material.

**Proof of Theorem 2.** The claim follows upon an application of the fundamental Theorem 5 of the supplemental material [23, Theorem 23.9]. To verify its conditions, we use our Theorem 1 and Theorem 3.6.1 of [24].

**Proof of Lemma 3.** Let \( V \) be the diagonal matrix with \( \text{diag}(V) = \text{diag}(C^\top \Sigma_{p,q} C) \). As a consequence of Theorem 2, Lemma 3 and Slutsky's lemma, we have

\[
\sup_{x \in \mathbb{R}} \left| \Pr \left[ \left\{ \langle S_n^* \rangle \leq x \mid \xi_1, \ldots, \xi_{n_1}, \eta_1, \ldots, \eta_{n_2} \right\} - \Pr \left[ \left\{ \langle V^{-1/2} C^\top w_{p,q} \rangle \leq x \right\} \right] \right| \to 0
\]

as \( n \to \infty \), in probability [7, p. 862]. Hence, for all \( \theta_{p,q} \) such that \( \langle c_{i_1}, \theta_{p,q} \rangle = \ldots = \langle c_{i_m}, \theta_{p,q} \rangle = 0 \),

\[
\Pr \left( \bigcup_{j=1}^m \{ \langle q_{j,\delta} \rangle = 1 \} \right) = \Pr \left( \max_{\{j \in \{1, \ldots, i_m\} \}} |T_{j,n}| > q_{1, \ldots, n}(S_n^*; 1-\delta) \right)
\leq \Pr \left( \max_{\{j \in \{1, \ldots, i_m\} \}} |T_{j,n}| > q_{1, \ldots, n}(S_n^*; 1-\delta) \right)
= \Pr \left( \max_{\{j \in \{1, \ldots, i_m\} \}} \left\{ n^{1/2} \left( \langle c_j, \theta_{p,q} \rangle (P_{n}) - \langle c_j, \theta_{p,q} \rangle (P) \right) \right\} > q_{1, \ldots, n}(S_n^*; 1-\delta) \right) \to \delta
\]

as \( n \to \infty \), where \( q_{1, \ldots, n}(S_n^*; 1-\delta) \) denotes the \((1-\delta)\) the equi-coordinate quantile of \( \left( \langle S_n^* \rangle, \ldots, \langle S_n^* \rangle \right)^\top \). For the global test, i.e. if \( \{i_1, \ldots, i_m\} = \{1, \ldots, r\} \), the inequality in the second line becomes an equality.
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Appendix A. Supplemental Material

Details of the proof of Lemma 1

For the Lebesgue–Stieltjes measure of a càdlàg function $F$, we write $\mu_F$. Without loss of generality we consider the case $i = 1$. Let us first estimate the size of $D_{1,r}^{(1)}$. We have

$$t_r D_{1,r}^{(1)} = \int_{[a+yt_r,b+yt_r]} [G_1 + t_r h_{x+1,r}] (b + yt_r) - [G_1 + t_r h_{x+1,r}] (u) \ d[F_1 + t_r h_{1,r}](u)$$

$$- \int_{[a,b]} [G_1 + t_r h_{x+1,r}] (b) - [G_1 + t_r h_{x+1,r}] (u) \ d[F_1 + t_r h_{1,r}](u)$$

$$= \int_{(-\infty,b+yt_r]} [G_1 + t_r h_{x+1,r}] (b + yt_r) - [G_1 + t_r h_{x+1,r}] (u) \ d[F_1 + t_r h_{1,r}](u)$$

$$- \int_{(-\infty,a+yt_r]} [G_1 + t_r h_{x+1,r}] (b + yt_r) - [G_1 + t_r h_{x+1,r}] (u) \ d[F_1 + t_r h_{1,r}](u)$$

$$- \int_{(-\infty,b]} [G_1 + t_r h_{x+1,r}] (b) - [G_1 + t_r h_{x+1,r}] (u) \ d[F_1 + t_r h_{1,r}](u)$$

$$- \int_{(-\infty,a+yt_r]} [G_1 + t_r h_{x+1,r}] (b) - [G_1 + t_r h_{x+1,r}] (u) \ d[F_1 + t_r h_{1,r}](u)$$

$$+ \int_{(-\infty,a]} [G_1 + t_r h_{x+1,r}] (b) - [G_1 + t_r h_{x+1,r}] (u) \ d[F_1 + t_r h_{1,r}](u).$$

As $r \to \infty$, we see that

$$\frac{1}{yt_r} \int_{(-\infty,b+yt_r]} [G_1 + t_r h_{x+1,r}] (b + yt_r) - [G_1 + t_r h_{x+1,r}] (u) \ d[F_1 + t_r h_{1,r}](u)$$

$$= \left[ \frac{G_1(b + yt_r) - G_1(b)}{yt_r} + \frac{h_{x+1,r}(b+yt_r) - h_{x+1,r}(b)}{y} \right] \left[ F_1(b + t_r y) + t_r \mu_{h_{1,r}} ((-\infty,b + t_r y)] \right]$$

$$= (g_1(b) + o(1)) \left( F_1(b) + o(1) + O(t_r) \right),$$

and analogously

$$\frac{1}{yt_r} \int_{(-\infty,a+yt_r]} [G_1 + t_r h_{x+1,r}] (b + yt_r) - [G_1 + t_r h_{x+1,r}] (u) \ d[F_1 + t_r h_{1,r}](u)$$

$$= (g_1(b) + o(1)) \left( F_1(a) + o(1) + O(t_r) \right).$$

If $r$ is large enough, both $F_1$ and $G_1$ are continuously differentiable in $(b - |yt_r|, b + |yt_r|)$. Therefore,

$$\frac{1}{yt_r} \int_{(-\infty,b+yt_r]} (G_1(b) - G_1(u)) \ dF_1(u) = \frac{1}{yt_r} \int_{(-\infty,b]} (G_1(b) - G_1(u)) \ dF_1(u)$$

$$= (g_1(b) + o(1)) \left( F_1(b) + o(1) + O(t_r) \right).$$
for some \( z_r \in \mathbb{R} \) with \( |z_r - b| \leq |y t_r| \). Hence,

\[
\frac{1}{y t_r} \int_{(-\infty,b+yt_r)} \bigg[ (G_1 + t_r h_{k+1,r})(b) - (G_1 + t_r h_{k+1,r})(u) \bigg] \, d(F_1 + t_r h_{1,r})(u)
- \int_{(-\infty,b]} \big( G_1 + t_r h_{k+1,r} \big)(b) - \big( G_1 + t_r h_{k+1,r} \big)(u) \, d(F_1 + t_r h_{1,r})(u)
\leq \frac{1}{y t_r} \int_{(-\infty,b+yt_r]} \big[ G_1(b) - G_1(u) \big] \, dF_1(u) - \frac{1}{y t_r} \int_{(-\infty,b]} \big[ G_1(b) - G_1(u) \big] \, dF_1(u)
+ \frac{2}{y} \sup_{\mu_{h_{1,r}}} \| h_{k+1,r} \| \mu_{F_1} \left( (b, b + y t_r] \cup (b + y t_r, b) \right) + \frac{2 + o(1)}{y} \mu_{h_{1,r}} \left( (b, b + y t_r] \cup (b + y t_r, b) \right)
= |G_1(b) - G_1(z_k)| |f_1(z_k)| + o(1)
= o(1)
\]

for \( k \to \infty \). Analogously we infer that

\[
\frac{1}{x t_r} \int_{(-\infty,a+xt_r]} \bigg[ (G_1 + t_r h_{k+1,r})(b) - (G_1 + t_r h_{k+1,r})(u) \bigg] \, d(F_1 + t_r h_{1,r})(u)
- \int_{(-\infty,a]} \big( G_1 + t_r h_{k+1,r} \big)(b) - \big( G_1 + t_r h_{k+1,r} \big)(u) \, d(F_1 + t_r h_{1,r})(u)
= (G_1(b) - G_1(a)) f_1(a) + o(1),
\]
as \( r \to \infty \). In summary, we have shown so far that

\[
\lim_{r \to \infty} \left| D^{(1)}_{1,r} - \left[ y g_1(b)[F_1(b) - F_1(a)] - x f_1(a)[G_1(b) - G_1(a)] \right] \right| = 0.
\]

As for \( D^{(2)}_{1,k} \), we see that

\[
D^{(2)}_{1,r} = \frac{1}{t_r} \int_{[a,b]} \big[ (G_1 + t_r h_{k+1,r})(b) - (G_1 + t_r h_{k+1,r})(u) \big] \, d(F_1 + t_r h_{1,r})(u)
- \int_{[a,b]} \big( G_1(b) - G_1(u) \big) \, dF_1(u)
\]

\[
= \int_{[a,b]} \left( h_{k+1,r}(b) - h_{k+1,r}(u) \right) \, dF_1(u)
+ \int_{[a,b]} \left( G_1(b) - G_1(u) \right) \, dF_1(u)
+ t_r \int_{[a,b]} \left( h_{k+1,r}(b) - h_{k+1,r}(u) \right) \, dF_1(u)
= \int_{[a,b]} \left( h_{k+1,b} - h_{k+1,u} \right) \, dF_1(u)
+ \int_{[a,b]} \left( h_{1,r}(u) - h_{1,r}(a) \right) \, dG_1(u)
+ O(t_r)
= \int_{[a,b]} \left( h_{k+1,b} - h_{k+1,u} \right) \, dF_1(u)
+ \int_{[a,b]} \left( h_{1,u} - h_{1,a} \right) \, dG_1(u) + o(1),
\]

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since \( \|h_{x+1,r} - h_{x+1}\|_\infty + \|h_{1,r} - h_1\|_\infty \to 0 \), as \( r \to \infty \).

Details of the proof of Lemma \(^2\)

Let \( P_{i,n}^{(0)} = \alpha_n^{-1} \sum_{r=1}^{n} \delta_{i_r} \) and \( P_{i,n}^{(1)} = \beta_n^{-1} \sum_{r=1}^{n} \delta_{\eta_r} \). Recall that

\[
\hat{a}_{p,q,j} = \frac{\alpha_n + \beta_n}{\alpha_n} \int_{[a_{i_p},b_{i_p}]} \int_{[a_{j_q},b_{j_q}]} (F_n(k_{i,j}(u,v)) - F_{i,n}(u)F_{j,n}(v)) \text{d}G_{i,n}(v) \text{d}G_{j,n}(u)
+ \frac{\alpha_n + \beta_n}{\beta_n} \int_{[a_{i_p},b_{i_p}]} \int_{[a_{j_q},b_{j_q}]} (G_n(k_{i,j}(u,v)) - G_{i,n}(u)G_{j,n}(v)) \text{d}F_{i,n}(v) \text{d}F_{j,n}(u). \quad (A.1)
\]

We consider both addends separately. As for the first term, observe that

\[
\left| \frac{\alpha_n + \beta_n}{\alpha_n} \int_{[a_{i_p},b_{i_p}]} \int_{[a_{j_q},b_{j_q}]} (F_n(k_{i,j}(u,v)) - F_{i,n}(u)F_{j,n}(v)) \text{d}G_{i,n}(v) \text{d}G_{j,n}(u)
- \frac{1}{\lambda} \int_D (F(k_{i,j}(u,v)) - F_i(u)F_j(v)) P_i^{(1)} \otimes P_j^{(1)}(du, dv) \right|
\leq \left( \|F - F\|_\infty + \|F_{i,n} - F_i\|_\infty \right) P_i^{(1)} \text{d}F_j^{(1)}(a_{i_p}, b_{i_p}) P_j^{(1)}(a_{j_q}, b_{j_q})
+ \left( \|P_{i,n}^{(1)}(a_{i_p}, b_{i_p}) \|_\infty - P_i^{(1)}(a_{i_p}, b_{i_p}) \|_\infty \right) P_j^{(1)}(a_{j_q}, b_{j_q})
+ \int_{R^2} \left| F_{i,n} - F_i \right| F_{j,n} \text{d}F_j \otimes P_i^{(1)}(du, dv)
+ \left| P_i^{(1)} \right| P_j^{(1)} \otimes P_i^{(1)}(R^2)
+ o(1).
\]

The first two addends and the last one converge to zero almost surely as a consequence of the Gliwenko–Cantelli theorem. As for the third term, we note that \( \hat{a}_{i_p} \to a_i \) almost surely and analogously for the other quantiles. Therefore, after applying Lebesgue’s dominated convergence theorem, we infer that the third term converges to zero as well, and we conclude that

\[
\left| \frac{\alpha_n + \beta_n}{\alpha_n} \int_{[a_{i_p},b_{i_p}]} \int_{[a_{j_q},b_{j_q}]} (F_n(k_{i,j}(u,v)) - F_{i,n}(u)F_{j,n}(v)) \text{d}G_{i,n}(v) \text{d}G_{j,n}(u)
- \frac{1}{\lambda} \int_D (F(k_{i,j}(u,v)) - F_i(u)F_j(v)) P_i^{(1)} \otimes P_j^{(1)}(du, dv) \right| \to 0
\]
as \( n \to \infty \), with probability one. The other addend in line \( (A.1) \) is treated analogously.

Weak convergence of empirical processes

**Definition 9.** For \( n \in \mathbb{N} \), let \( X_n : \Omega \to \ell^\infty_{\infty}(d\omega) \) be \((\mathcal{F} - \mathcal{B}(\ell^\infty_{\infty}))\)-measurable, and let \( X_0 \) be \((\mathcal{F} - \mathcal{B}(\ell^\infty_{\infty}))\)-measurable. The sequence \( (X_n)_{n \in \mathbb{N}} \) is said to converge weakly to \( X_0 \), denoted by \( X_n \rightharpoonup X_0 \), if for every bounded continuous
functional \( f: (\ell^\infty, d^\infty) \to \mathbb{R} \)

\[
\int f(X_n) d\Pr \to \int f(X_0) d\Pr \quad (n \to \infty).
\]

Here, \( f^*(X_n) d\Pr = \inf \{ \int U d\Pr: f(X_n) \leq U, U: (\Omega, \mathcal{F}) \to [\overline{\mathbb{R}}, \overline{\mathbb{R}}] \} \).

As in the classical theory, this form of weak convergence is characterized as convergence of the finite dimensional distributions plus tightness.

**Definition 10.** The random element \( X_0 \) is tight if for every \( \varepsilon > 0 \) there exists a compact \( K \subset (\ell^\infty, d^\infty) \) such that \( \Pr[X_0 \in K] > 1 - \varepsilon \).

The sequence \( \{X_n\} \) is asymptotically tight if for any \( \varepsilon > 0 \) there is a compact \( K \subset (\ell^\infty, d^\infty) \) such that \( \inf_{\delta > 0} \liminf_{n \to \infty} \Pr^* \{ \|X_n - K\| < \delta \} > 1 - \varepsilon \), where \( \Pr^* (B) := \inf \{ \Pr (A): B \subset A, A \in \mathcal{F} \} \) for \( B \subset (\ell^\infty, d^\infty) \).

The sequence \( \{X_n\} \) is asymptotically Borel measurable if

\[
\int f(X_n) d\Pr - \int f(X_n) d\Pr \to 0 \quad (n \to \infty),
\]

for every bounded continuous functional \( f \) on \( (\ell^\infty, d^\infty) \). Here, \( \int f(X_n) d\Pr := \sup \{ \int f d\Pr: L \leq f, L: (\Omega, \mathcal{F}) \to (\mathbb{R}, \mathcal{B}) \} \).

**Lemma 4.** Let \( \{P_n\}_{n \in \mathbb{N}} \) be a sequence of probability measures on \( (\ell^\infty, \mathcal{B}(\ell^\infty)) \) and \( P_0 \) a Borel probability measure on \( (\ell^\infty, \mathcal{B}(\ell^\infty)) \), respectively. Furthermore, let \( \{Y_n\}_{n \in \mathbb{N}} \) be a sequence of random elements \( Y_n: (\Omega, \mathcal{F}) \to (\ell^\infty, \mathcal{B}(\ell^\infty)) \) and \( Y_0: (\Omega, \mathcal{F}) \to (\ell^\infty, \mathcal{B}(\ell^\infty)) \). Suppose that \( P_n = \Pr Y_n^{-1} \) for all \( n \in \mathbb{N} \). If \( \lim_{n \to \infty} \int f dP_n = \int f dP_0 \) for every bounded continuous functional \( f \) on \( (\ell^\infty, d^\infty) \), then \( Y_n \Rightarrow Y_0 \).

**Proof.** First note that \( \int f dP_n - \int f dP_0 \) implies \( \int f dP_n - \int f dP_n \to 0 \) [24, Lemma 1.3.8]. The following chain of inequalities holds for any \( n \in \mathbb{N}_+ \) and all bounded continuous functional \( f \) on \( \ell^k \):

\[
\int f dP_n = \inf \left\{ \int T dP_n: T \equiv f, T: \ell^\infty \to (\mathbb{R}, \mathcal{B}) \right\} \\
\geq \inf \left\{ \int T \circ Y_n d\Pr: T \circ Y_n \equiv f \circ Y_n, T: \ell^\infty \to (\mathbb{R}, \mathcal{B}) \right\} \\
= \sup \left\{ \int S d\Pr: S \equiv f \circ Y_n, S: (\Omega, \mathcal{F}) \to (\mathbb{R}, \mathcal{B}) \right\} \\
= \int f dP_n.
\]

Therefore, \( \int f dP_n \leq \int f(Y_n) d\Pr \leq \int f dP_n \), and \( \lim_{n \to \infty} \int f(Y_n) d\Pr \) exists and equals \( \lim_{n \to \infty} \int f dP_n \). Hence, \( Y_n \Rightarrow Y_0 \).

**Theorem 4** (van der Vaart and Wellner [24], p. 35). Let \( k = 1 \). If the sequence \( \{X_n\}_{n \in \mathbb{N}_+} \) is asymptotically tight and for any \( t_1, \ldots, t_r \in \mathbb{R} \) and \( r \in \mathbb{N} \)

\[
(\pi_{t_1} \circ X_n, \ldots, \pi_{t_r} \circ X_n) \Rightarrow (\pi_{t_1} \circ X_0, \ldots, \pi_{t_r} \circ X_0)
\]

in \( \mathbb{R}^r \), then \( X_n \Rightarrow X_0 \) in \( (\ell^\infty, d^\infty) \) and the limit \( X_0 \) is a Borel measurable tight random element.
Empirical bootstrap fundamental theorem

**Theorem 5** (van der Vaart and Wellner [24], Thm. 23.9). Let $D$ be a normed space and denote by $BL_1(D)$ the set of bounded Lipschitz functions on $D \rightarrow [-1,1]$ with Lipschitz constant at most 1. Suppose that the map $\phi : D_0 \subset D \rightarrow \mathbb{R}^\kappa$ is Hadamard differentiable at $\theta$ tangentially to a subspace $D_0$. Let $\hat{\theta}_n$ and $\hat{\theta}_n^*$ be maps with values in $D_0$ such that $n^{1/2}(\hat{\theta}_n - \theta) \Rightarrow T$, with a tight $D_0$-valued random element $T$. Suppose that

$$
\sup_{h \in BL_1(D)} \left| E[h(n^{1/2}(\hat{\theta}_n^* - \hat{\theta}_n)) \mid \xi_1, \ldots, \xi_n] - Eh(T) \right| \rightarrow 0
$$

in outer probability and that $n^{1/2}(\hat{\theta}_n^* - \hat{\theta}_n)$ is asymptotically measurable. Then

$$
\sup_{h \in BL_1(\mathbb{R}^\kappa)} \left| E[h(n^{1/2}(\phi(\hat{\theta}_n^*) - \phi(\hat{\theta}_n))) \mid \xi_1, \ldots, \xi_n] - Eh(D\phi(\theta)[T]) \right| \rightarrow 0
$$

in outer probability.