

Computationally efficient and statistically accurate conditional independence testing with spaCRT

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Abstract

We introduce the saddlepoint approximation-based conditional randomization test (spaCRT), a novel conditional independence test that effectively balances statistical accuracy and computational efficiency, inspired by applications to single-cell CRISPR screens. Resampling-based methods like the distilled conditional randomization test (dCRT) offer statistical precision but at a high computational cost. The spaCRT leverages a saddlepoint approximation to the resampling distribution of the dCRT test statistic, achieving very similar finite-sample statistical performance with significantly reduced computational demands. We prove that the spaCRT p -value approximates the dCRT p -value with vanishing relative error, and that these two tests are asymptotically equivalent. Through extensive simulations and real data analysis, we demonstrate that the spaCRT controls Type-I error and maintains high power, outperforming other asymptotic and resampling-based tests. Our method is particularly well-suited for large-scale single-cell CRISPR screen analyses, facilitating the efficient and accurate assessment of perturbation-gene associations.

1 Introduction

Motivated by applications to *single-cell CRISPR screen* data analysis, we propose a resampling-free approximation to a resampling-based conditional independence test, the *distilled conditional randomization test* (dCRT; Liu et al., 2022). In doing so, we arrive at a test that has the finite-sample statistical performance of a resampling-based procedure and the speed of an asymptotic test.

1.1 Motivating application: Single-cell CRISPR screens

This work is motivated by the analysis of *single-cell CRISPR screen* data (Dixit et al., 2016; Adamson et al., 2016; Jaitin et al., 2016; Datlinger et al., 2017). In these experiments, one of the biological objectives is to understand *regulatory elements*, segments of DNA whose role is to control the expressions of one or more nearby genes. In particular, it is of interest to determine *which* regulatory elements control the expressions of *which* genes. This is a crucial question in understanding the genetic basis of human diseases, many of which are caused by genetic variants disrupting

regulatory elements and therefore causing abnormal gene expression. To address this question, single-cell CRISPR screens are designed to subject a population of cells to a large number of *CRISPR perturbations*, each of which inhibits the functioning of a specific regulatory element. Each cell receives several of these perturbations, and the expression of each gene in each cell is measured by single-cell RNA-sequencing. The statistical analysis task is to determine, for each CRISPR perturbation and gene of interest, whether cells with the perturbation have different gene expression levels compared to cells without the perturbation. To translate this into statistical language, let random variables $\mathbf{X} \in \{0, 1\}$, $\mathbf{Y} \in \mathbb{N}$, and $\mathbf{Z} \in \mathbb{R}^p$ represent the presence of a CRISPR perturbation, the gene expression level, and a set of covariates measured in a cell, respectively. The covariates \mathbf{Z} include technical factors like library size (the total number of RNA molecules sequenced in a cell) and experimental batch, which may impact both \mathbf{X} and \mathbf{Y} (Barry et al., 2021). In the joint distribution $(\mathbf{X}, \mathbf{Y}, \mathbf{Z}) \sim \mathcal{L}_n$ (potentially depending on the number of cells n), the statistical task is to test the null hypothesis

$$H_0 : \mathbf{X} \perp\!\!\!\perp \mathbf{Y} \mid \mathbf{Z}, \quad (1)$$

i.e., that the presence of the CRISPR perturbation is conditionally independent of the gene expression level, given the covariates. To this end, we collect observations $(X_{in}, Y_{in}, Z_{in}) \stackrel{\text{i.i.d.}}{\sim} \mathcal{L}_n$ for cells $i = 1, \dots, n$. We denote these observations collectively as $X \in \mathbb{R}^n$, $Y \in \mathbb{R}^n$, $Z \in \mathbb{R}^{n \times p}$.

1.2 Statistical and computational challenges

One challenging aspect of this problem is that both X and Y are highly sparse. Indeed, due to the pooling of a large number of perturbations in a single experiment, most perturbations are present in only a small fraction of cells. Furthermore, gene expression data are measured as RNA molecule counts, and when measured at single-cell resolution, the relatively small number of total RNA molecules measured per cell and the large number of genes result in many genes having zero expression in most cells (Svensson, 2020). As a result, the effective sample size for testing H_0 is relatively small, which can cause asymptotic tests based on the central limit theorem to have inflated Type-I error rates (Barry et al., 2024). To address this challenge, we have proposed to apply the resampling-based *conditional randomization test* (CRT; Candès et al., 2018). More specifically, we have employed an accelerated variant of the CRT called the dCRT (Liu et al., 2022), coupled with a negative binomial regression-based test statistic, for single-cell CRISPR screen analysis (Barry et al., 2021). The resulting method (SCEPTRE) and the associated R package (**sceptre**) are considered the state of the art for perturbation-gene association testing in single-cell CRISPR screens, and have been employed in several recent studies (Morris et al., 2023; Tuano et al., 2023; Chardon et al., 2023; Conery et al., 2024).

Although the dCRT is much faster than the originally proposed variant of the CRT, it is still a resampling-based procedure, which poses computational challenges for large-scale applications like single-cell CRISPR screens. For example, Gasperini et al. (2019) tested about 90,000 perturbation-gene pairs. Given the multiplicity correction required for such a large number of tests, p -values need to be accurate to about seven decimal places to have a chance at significance (assuming a Bonferroni correction at level $\alpha =$

0.05). Obtaining such accurate p -values requires about a million resamples per p -value, for a total of about 10^{12} resamples across all perturbation-gene pairs tested. Even with parallelization, this becomes quite a computationally intensive task. Therefore, we arrive at an apparent impasse: asymptotic methods are fast but inaccurate, while resampling-based methods are accurate but slow.

1.3 Our contributions

We propose a new method, the *saddlepoint approximation-based conditional randomization test* (spaCRT), which reconciles the statistical accuracy of the dCRT with the computational efficiency of asymptotic methods. The key idea is to approximate the distribution of the resampled test statistic in the dCRT using a *saddlepoint approximation* (SPA; Daniels, 1954; Lugannani and Rice, 1980), a classical technique to obtain highly accurate approximations to densities and tail probabilities for quantities that can be expressed as sample averages. To preview the statistical and computational performance of the spaCRT, we present the analysis of the Gasperini et al. (2019) single-cell CRISPR screen dataset (Figure 1). In this analysis, we compare the spaCRT to the generalized covariance measure (GCM) test (Shah and Peters, 2020) (a conditional independence test based on asymptotic normality) and the dCRT using $M = 100,000$ resamples (for details on this analysis, see Section 5). We find that the spaCRT is more than two orders of magnitude faster than the dCRT while maintaining Type-I error control, unlike the GCM test. We prove under relatively mild assumptions that the spaCRT p -value has vanishing relative error compared to the dCRT p -value, and that the two tests are asymptotically equivalent. We demonstrate the statistical and computational advantages of the spaCRT using extensive numerical simulations as well as an analysis of the Gasperini et al. (2019) data. Code to reproduce these analyses is available at github.com/Katsevich-Lab/spacrt-manuscript.

For single-cell CRISPR screen applications, the spaCRT can be used to significantly accelerate the `sceptre` software without compromising its statistical performance, facilitating the analysis of much larger datasets than previously possible. Beyond single-cell CRISPR screens, the conditional independence testing problem is a ubiquitous one, and the spaCRT points the way towards a new class of fast and accurate tests.

1.4 Related work

In the same paper where the dCRT was introduced (Liu et al., 2022), a resampling-free approximation to this procedure was proposed based on a quantile transformation to a normal distribution. However, these authors acknowledged that this approach is primarily useful for continuously distributed \mathbf{X} , and that it incurs a substantial power loss for discrete \mathbf{X} , the setting we are focused on in the present work. SPAs have been proposed to approximate resampling distributions of other resampling-based procedures, like permutation tests (Robinson, 1982) and the bootstrap (Davison and Hinkley, 1988). However, to the best of our knowledge, the spaCRT is the first application of SPA to a conditional independence test. Furthermore, existing applications of the SPA to resampling-based procedures have not been rigorously justified, a gap we address in a parallel work (Niu, Ray Choudhury, and Katsevich, 2024). In

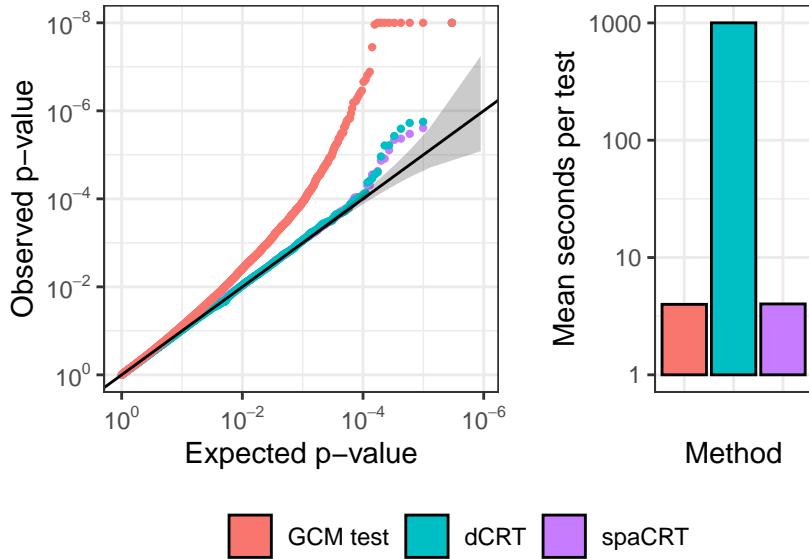


Figure 1: Comparing the Type-I error control and computation times of the GCM test, the dCRT and the proposed spaCRT on the Gasperini et al. (2019) data. We use logistic regression to model the perturbation $\mathbf{X}|\mathbf{Z}$ and negative binomial regression to model the outcome $\mathbf{Y}|\mathbf{Z}$. Left: QQ-plot of the p -values under the null hypothesis, obtained from testing 51 *non-targeting* perturbations against 3,000 genes. The p -values are truncated from below at 10^{-8} for visualization purposes. Right: Mean computation times per perturbation-gene pair, in seconds.

a different strand of work, resampling-based procedures have been accelerated using adaptive resampling schemes, which adjust the number of resamples drawn based on the data (Besag and Clifford, 1991; Gandy, 2009; Gandy and Hahn, 2014; Gandy and Hahn, 2016; Gandy and Hahn, 2017; Fischer and Ramdas, 2024b; Fischer and Ramdas, 2024a). Such procedures are applicable to arbitrary resampling schemes and test statistics, at the cost of some resampling. In contrast, the spaCRT is a completely resampling-free procedure, though more specialized in its application.

1.5 Outline of the paper

We introduce the spaCRT in Section 2. We present the theoretical properties of the spaCRT in Section 3. We demonstrate the performance of the spaCRT in a simulation study in Section 4. We apply the spaCRT to the Gasperini et al. (2019) data in Section 5. We conclude with a discussion in Section 6.

1.6 Notation

Define $\text{sgn}(x)$ as the sign of x , i.e. $\text{sgn}(x) = 1$ if $x > 0$, -1 if $x < 0$ and 0 otherwise. For an infinitely differentiable function $f : \mathcal{X} \subset \mathbb{R} \mapsto \mathbb{R}$, define $f^{(r)}$ to be its r -th derivative. Define f' , f'' as the first and second derivative of f respectively. Denote $[n]$ for any $n \in \mathbb{N}_+$ as $\{1, \dots, n\}$. Define $\text{expit}(x) \equiv 1/(1 + \exp(-x))$. Define $\mathbb{E}_{\mathcal{L}_n}[\cdot | \mathcal{F}_n]$, $\mathbb{E}_{\widehat{\mathcal{L}}_n}[\cdot | \mathcal{F}_n]$ as the conditional expectations under law \mathcal{L}_n and its estimate $\widehat{\mathcal{L}}_n$ respectively. Similarly,

we define $\text{Var}_{\mathcal{L}_n}[\cdot \mid \mathcal{F}_n]$ and $\text{Var}_{\widehat{\mathcal{L}}_n}[\cdot \mid \mathcal{F}_n]$ as the conditional variance counterpart. We use the following standard notations regarding the asymptotic properties of a sequence of random variables X_n :

$$\begin{aligned} X_n = O_{\mathbb{P}}(1) &\quad \text{if for each } \delta > 0 \text{ there is an } M > 0 \text{ s.t. } \limsup_{n \rightarrow \infty} \mathbb{P}[|X_n| > M] < \delta; \\ X_n = \Omega_{\mathbb{P}}(1) &\quad \text{if for each } \delta > 0 \text{ there is an } \eta > 0 \text{ s.t. } \limsup_{n \rightarrow \infty} \mathbb{P}[|X_n| < \eta] < \delta; \\ X_n = o_{\mathbb{P}}(1) &\quad \text{if } \mathbb{P}[|X_n| > \eta] \rightarrow 0 \text{ for all } \eta > 0. \end{aligned}$$

2 spaCRT: A resampling-free approximation to dCRT

2.1 Background: dCRT

The original dCRT procedure, as proposed by Liu et al. (2022), is designed under the *model-X assumption* that $\mathcal{L}_n(\mathbf{X} \mid \mathbf{Z})$ is known (Candès et al., 2018). However, this procedure is usually deployed in practice by learning this conditional distribution in-sample. In a prior work, we established the statistical properties of the dCRT with $\mathcal{L}_n(\mathbf{X} \mid \mathbf{Z})$ estimated in sample (Niu et al., 2024). In this paper, we will refer to the latter procedure as the dCRT, allowing a minor abuse of terminology. Furthermore, we consider the special case when

$$\mathcal{L}_n(\mathbf{X} \mid \mathbf{Z}) = f(\mathbf{X} \mid \theta_{n,x}(\mathbf{Z})), \quad (2)$$

where $f(x|\theta)$ is an exponential family with natural parameter θ , natural parameter space \mathbb{R} , and log-partition function A :

$$f(x|\theta) = \exp(\theta x - A(\theta))h(x).$$

This is not a restrictive assumption, since we allow the function $\theta_{n,x}(\mathbf{Z})$ to be arbitrary. Given this setup, consider estimating the functions $\theta_{n,x}(\mathbf{Z})$ and $\mu_{n,y}(\mathbf{Z}) \equiv \mathbb{E}_{\mathcal{L}_n}[\mathbf{Y} \mid \mathbf{Z}]$ by $\widehat{\theta}_{n,x}(\mathbf{Z})$ and $\widehat{\mu}_{n,y}(\mathbf{Z})$, respectively (we assume throughout that \mathbf{Y} is integrable, so that $\mu_{n,y}$ is well-defined). The learning procedures for these quantities can be arbitrary. Setting $\widehat{\mu}_{n,x}(\mathbf{Z}) \equiv A'(\widehat{\theta}_{n,x}(\mathbf{Z}))$, we arrive at the test statistic

$$T_n^{\text{dCRT}}(X, Y, Z) = \frac{1}{n} \sum_{i=1}^n (X_{in} - \widehat{\mu}_{n,x}(Z_{in}))(Y_{in} - \widehat{\mu}_{n,y}(Z_{in})). \quad (3)$$

The dCRT is obtained by comparing $T_n^{\text{dCRT}}(X, Y, Z)$ to a null distribution obtained by resampling $X_{in} \mid Z_{in}$ based on the estimated distribution $f(\cdot \mid \widehat{\theta}_{n,x}(Z_{in}))$. This procedure is summarized in Algorithm 1.

The dCRT (Algorithm 1) has many desirable statistical properties which make it a suitable choice for testing conditional independence. First, it is a resampling-based test and thus can potentially improve finite-sample performance compared to its asymptotic counterpart, the GCM test, which relies on asymptotic normality. While this improvement is quite evident in practice (recall Figure 1), the theoretical basis for this improvement has not yet been established; this interesting research direction is beyond

the scope of the current work. Moreover, the dCRT allows flexible in modeling choices: the estimator $\hat{\mu}_{n,y}(\cdot)$ of the conditional expectation $\mathbb{E}[Y | Z = \cdot]$ can be constructed by any regression method. The choices include but are not limited to parametric, non-parametric and high-dimensional regression methods. Another desirable property for dCRT is its so-called double robustness property. As long as both estimators $\hat{\mu}_{n,x}(\cdot)$ and $\hat{\mu}_{n,y}(\cdot)$ are consistent and converge to the true conditional expectations at rate faster than $n^{-1/4}$, the validity of the test can be guaranteed (Niu et al., 2024, Corollary 3). The proposed method can be applied to approximate the dCRT procedure with any such estimators, even though our motivating real data analysis for single-cell CRISPR screens focuses on generalized linear models.

Algorithm 1: dCRT procedure with exponential family for $\mathcal{L}_n(X | Z)$

Input: Data (X, Y, Z) , number of randomizations M .

- 1 Learn $\hat{\theta}_{n,x}(\cdot)$ and $\hat{\mu}_{n,x}(\cdot)$ based on (X, Z) ; learn $\hat{\mu}_{n,y}(\cdot)$ based on (Y, Z) ;
- 2 Compute $T_n^{\text{dCRT}}(X, Y, Z)$ as in (3);
- 3 **for** $m = 1, 2, \dots, M$ **do**
- 4 Sample $\tilde{X}^{(m)} | X, Y, Z \sim \prod_{i=1}^n f(\cdot | \hat{\theta}_{n,x}(Z_{in}))$ and compute

$$T_n^{\text{dCRT}}(\tilde{X}^{(m)}, X, Y, Z) \equiv \frac{1}{n} \sum_{i=1}^n (\tilde{X}_{in}^{(m)} - \hat{\mu}_{n,x}(Z_{in}))(Y_{in} - \hat{\mu}_{n,y}(Z_{in})); \quad (4)$$
- 5 **end**

Output: dCRT p -value

$$\frac{1}{M+1} (1 + \sum_{m=1}^M \mathbb{1}\{T_n^{\text{dCRT}}(\tilde{X}^{(m)}, X, Y, Z) \geq T_n^{\text{dCRT}}(X, Y, Z)\}).$$

2.2 The spaCRT

If we consider the limit of the dCRT p -value as the number of resamples M grows indefinitely, we obtain

$$p_{\text{dCRT}} \equiv \mathbb{P} \left[T_n^{\text{dCRT}}(\tilde{X}, X, Y, Z) \geq T_n^{\text{dCRT}}(X, Y, Z) \mid X, Y, Z \right].$$

We approximate this conditional tail probability via the SPA. Note that the resampled test statistic defined in (4) is the mean of conditionally independent random variables:

$$T_n^{\text{dCRT}}(\tilde{X}^{(m)}, X, Y, Z) \equiv \frac{1}{n} \sum_{i=1}^n W_{in}, \quad W_{in} \equiv a_{in}(\tilde{X}_{in} - \hat{\mu}_{n,x}(Z_{in})), \quad a_{in} \equiv Y_{in} - \hat{\mu}_{n,y}(Z_{in}).$$

Indeed, W_{in} are independent, but not identically distributed, conditionally on the σ -algebra $\mathcal{F}_n \equiv \sigma(X, Y, Z)$. In a parallel work (Niu, Ray Choudhury, and Katsevich, 2024), we have established an SPA result for means of conditionally independent random variables under relatively mild conditions. This result is restated here as Lemma 6 in Appendix B. This result is expressed in terms of the average conditional cumulant-generating function

$$K_n(s | \mathcal{F}_n) \equiv \frac{1}{n} \sum_{i=1}^n K_{in}(s | \mathcal{F}_n) \equiv \frac{1}{n} \sum_{i=1}^n \log \mathbb{E}[\exp(sW_{in}) | \mathcal{F}_n], \quad (5)$$

which in our case can be expressed as

$$K_n(s \mid \mathcal{F}_n) = \frac{1}{n} \sum_{i=1}^n \left\{ A(\hat{\theta}_{n,x}(Z_{in}) + a_{in}s) - A(\hat{\theta}_{n,x}(Z_{in})) - a_{in}sA'(\hat{\theta}_{n,x}(Z_{in})) \right\}. \quad (6)$$

The first two derivatives of this quantity are

$$K'_n(s \mid \mathcal{F}_n) = \frac{1}{n} \sum_{i=1}^n a_{in} \left(A'(\hat{\theta}_{n,x}(Z_{in}) + a_{in}s) - A'(\hat{\theta}_{n,x}(Z_{in})) \right), \quad (7)$$

$$K''_n(s \mid \mathcal{F}_n) = \frac{1}{n} \sum_{i=1}^n a_{in}^2 A''(\hat{\theta}_{n,x}(Z_{in}) + a_{in}s). \quad (8)$$

We can now present the saddlepoint approximation-based conditional randomization test (spaCRT) procedure (Algorithm 2).

Algorithm 2: spaCRT procedure

Input: Data (X, Y, Z) .

- 1 Learn $\hat{\theta}_{n,x}(\cdot)$ and $\hat{\mu}_{n,x}(\cdot)$ based on (X, Z) , $\hat{\mu}_{n,y}(\cdot)$ based on (Y, Z) ;
- 2 Compute $T_n^{\text{dCRT}}(X, Y, Z)$ as in (3);
- 3 Find \hat{s}_n that solves the saddlepoint equation

$$K'_n(s \mid \mathcal{F}_n) = T_n^{\text{dCRT}}(X, Y, Z); \quad (9)$$

- 4 Compute $\lambda_n = \sqrt{n}\hat{s}_n\sqrt{K''_n(\hat{s}_n \mid \mathcal{F}_n)}$ and

$$r_n = \begin{cases} \text{sgn}(\hat{s}_n)\sqrt{2n(\hat{s}_n T_n^{\text{dCRT}} - K_n(\hat{s}_n \mid \mathcal{F}_n))}, & \text{if } \hat{s}_n T_n^{\text{dCRT}} - K_n(\hat{s}_n \mid \mathcal{F}_n) \geq 0; \\ \text{sgn}(\hat{s}_n) & \text{otherwise.} \end{cases}$$

Output: spaCRT p -value

$$p_{\text{spaCRT}} \equiv 1 - \Phi(r_n) + \phi(r_n) \left\{ \frac{1}{\lambda_n} - \frac{1}{r_n} \right\}. \quad (10)$$

The spaCRT procedure is attractive because it is completely resampling-free. It requires the following one-time computations: fitting the estimates $\hat{\theta}_{n,x}$ and $\hat{\mu}_{n,y}$, calculating the test statistic T_n^{dCRT} , and finding the solution to the saddlepoint equation (9). The latter is a one-dimensional root-finding problem and can be solved efficiently using standard numerical optimization algorithms.

To make the spaCRT procedure more concrete, we provide an example in the case that \mathbf{X} is binary, a setting that matches our motivating application.

Example 1 (Bernoulli sampling). Suppose $\mathbf{X} \mid \mathbf{Z} \sim \text{Ber}(\mu_{n,x}(\mathbf{Z}))$, and $\theta_{n,x}(\mathbf{Z}) = \text{logit}(\mu_{n,x}(\mathbf{Z}))$. Then, we have $A(\theta) = \log(1 + \exp(\theta))$. After some manipulation, the saddlepoint equation reduces to

$$\frac{1}{n} \sum_{i=1}^n (Y_{in} - \hat{\mu}_{n,y}(Z_{in}))(X_{in} - \text{expit}(\hat{\theta}_{n,x}(Z_{in}) + s(Y_{in} - \hat{\mu}_{n,y}(Z_{in})))) = 0.$$

Defining $\tilde{\mu}_{n,x}(Z_{in}) \equiv \text{expit}(\hat{\theta}_{n,x}(Z_{in}) + \hat{s}_n(Y_{in} - \hat{\mu}_{n,y}(Z_{in})))$ for convenience, λ_n and r_n can be computed as

$$\lambda_n = \hat{s}_n \sqrt{\sum_{i=1}^n (Y_{in} - \hat{\mu}_{n,y}(Z_{in}))^2 \tilde{\mu}_{n,x}(Z_{in})(1 - \tilde{\mu}_{n,x}(Z_{in}))}$$

and

$$r_n = \text{sgn}(\hat{s}_n) \sqrt{2 \sum_{i=1}^n \left(X_{in} \log \frac{\tilde{\mu}_{n,x}(Z_{in})}{\hat{\mu}_{n,x}(Z_{in})} + (1 - X_{in}) \log \frac{1 - \tilde{\mu}_{n,x}(Z_{in})}{1 - \hat{\mu}_{n,x}(Z_{in})} \right)},$$

or simply $\text{sgn}(\hat{s}_n)$ if the quantity under the square root is negative. Putting these pieces together, the spaCRT p -value can be computed as in equation (10).

3 Theoretical properties of the spaCRT

In this section, we establish the theoretical properties of the spaCRT. We first state general results concerning the approximation accuracy of the spaCRT p -value and the asymptotic equivalence between the spaCRT and dCRT (Section 3.1). Then, we extract simpler and more concrete conditions in two special cases (Section 3.2).

3.1 General results

spaCRT does not require any resampling and thus has a significant advantage over dCRT in terms of computation. This advantage does not come with a sacrifice of statistical accuracy, as we will show in the following theorem.

Theorem 1 (Approximation accuracy). *Suppose there exists $S > 0$ such that **one** of the following conditions holds:*

$$\sup_i |\hat{\theta}_{n,x}(Z_{in})|, \sup_i |\hat{\mu}_{n,y}(Z_{in})| = O_{\mathbb{P}}(1), \mathbb{P}[Y_{in} \in [-S, S]] = 1 \text{ for any } i, n; \quad (\text{CSE})$$

$$\frac{1}{n} \sum_{i=1}^n (Y_{in} - \hat{\mu}_{n,y}(Z_{in}))^4 = O_{\mathbb{P}}(1), \mathbb{P}\left[\tilde{X}_{in} \in [-S, S]\right] = 1 \text{ for any } i, n. \quad (\text{CCS})$$

Suppose the following conditions hold:

$$|\hat{\theta}_{n,x}(Z_{in})| < \infty, |\hat{\mu}_{n,y}(Z_{in})| < \infty \text{ for any } i, n \text{ almost surely}; \quad (11)$$

$$\frac{1}{n} \sum_{i=1}^n (Y_{in} - \hat{\mu}_{n,y}(Z_{in}))^2 A''(\hat{\theta}_{n,x}(Z_{in})) = \Omega_{\mathbb{P}}(1); \quad (12)$$

$$T_n^{\text{dCRT}}(X, Y, Z) \xrightarrow{\mathbb{P}} 0. \quad (13)$$

Then, the saddlepoint equation (9) has a unique and finite solution $\hat{s}_n \in [-1/16, 1/16]$ with probability approaching 1 as $n \rightarrow \infty$. Furthermore, the spaCRT p -value p_{spaCRT} approximates the dCRT p -value p_{dCRT} with vanishing relative error:

$$p_{\text{dCRT}} = p_{\text{spaCRT}} \cdot (1 + o_{\mathbb{P}}(1)) \quad (14)$$

and spaCRT p -value is positive with probability approaching 1 as $n \rightarrow \infty$:

$$\mathbb{P}[p_{\text{spaCRT}} > 0] \rightarrow 1 \text{ as } n \rightarrow \infty. \quad (15)$$

To better understand the assumptions in Theorem 1, we provide the following remarks.

Remark 1 (Comments on the assumptions). Assumptions (CSE)-(CCS) are conditions that can be satisfied if the random variables involved have light enough tails and estimators $\hat{\theta}_{n,x}(Z_{in}), \hat{\mu}_{n,y}(Z_{in})$ are regular enough. Assumptions (11) and (12) are mild; their purpose is to rule out degenerate cases. Finally, the role of the assumption (13) is to guarantee the existence of the solution to the saddlepoint equation. This assumption allows the test statistic $T_n^{\text{dCRT}}(X, Y, Z)$ to converge to zero in probability, **at any rate**. In particular, we consider the following two most important cases among others:

1. **Under the null hypothesis:** Shah and Peters (2020) proved that under general conditions on $\hat{\mu}_{n,x}, \hat{\mu}_{n,y}, n^{1/2}T_n^{\text{dCRT}}(X, Y, Z)$ converges weakly to a normal distribution under the null hypothesis. Thus the condition (13) is satisfied under the null hypothesis with rate $n^{-1/2}$.
2. **Under contiguous local alternatives:** The proof of Theorem 3 in Niu et al. (2024) shows that under generalized partially linear models, the test statistic $n^{1/2}T_n^{\text{dCRT}}(X, Y, Z)$ converges to a normal distribution with nonzero mean and positive finite variance under local alternatives that are contiguous to the null distribution. Thus the condition is satisfied in this case with rate $n^{-1/2}$.

Remark 2 (Relative error guarantee). The relative error guarantee in conclusion (14) is a strong result. It means not only the difference of p -values is close to 0 with probability approaching 1, but also the ratio of p -values is close to 1 with probability approaching 1. This is a particularly desirable property for approximating small p -values.

It has been shown in Figure 1 that spaCRT and dCRT have similar statistical performance. This motivates us to understand the theoretical relationship between spaCRT and dCRT. To proceed with the statement of the results, we define the level- α tests associated with the dCRT and spaCRT p -values:

$$\phi_{n,\alpha}^{\text{dCRT}} \equiv \mathbb{1}(p_{\text{dCRT}} \leq \alpha) \quad \text{and} \quad \phi_{n,\alpha}^{\text{spaCRT}} \equiv \mathbb{1}(p_{\text{spaCRT}} \leq \alpha).$$

The following theorem states that these two tests are asymptotically equivalent.

Theorem 2. Suppose the assumptions of Theorem 1 hold. Fix $\alpha \in (0, 1)$. If the normalized test statistic $n^{1/2}T_n^{\text{dCRT}}(X, Y, Z)/\hat{S}_n^{\text{dCRT}}$, where \hat{S}_n^{dCRT} is defined in equation (31), does not accumulate around the $1 - \alpha$ quantile of standard normal distribution $z_{1-\alpha}$, i.e.,

$$\lim_{\delta \rightarrow 0} \limsup_{n \rightarrow \infty} \mathbb{P}_{\mathcal{L}_n} \left[\left| \frac{n^{1/2}T_n^{\text{dCRT}}(X, Y, Z)}{\hat{S}_n^{\text{dCRT}}} - z_{1-\alpha} \right| \leq \delta \right] = 0, \quad (16)$$

then the dCRT and spaCRT tests are asymptotically equivalent:

$$\lim_{n \rightarrow \infty} \mathbb{P}_{\mathcal{L}_n} [\phi_{n,\alpha}^{\text{spaCRT}} = \phi_{n,\alpha}^{\text{dCRT}}] = 1 \quad \text{and} \quad \lim_{n \rightarrow \infty} \mathbb{E}_{\mathcal{L}_n} [\phi_{n,\alpha}^{\text{spaCRT}}] - \mathbb{E}_{\mathcal{L}_n} [\phi_{n,\alpha}^{\text{dCRT}}] = 0.$$

Furthermore, the asymptotic Type-I error control of the spaCRT follows from that of the dCRT even without the regularity condition (16):

Corollary 1 (Asymptotic validity of spaCRT). *Suppose the assumptions of Theorem 1 hold. Fix $\alpha \in (0, 1)$. If $\lim_{n \rightarrow \infty} \mathbb{P}_{H_0}[p_{\text{dCRT}} \leq \alpha] \leq \alpha$, then we have*

$$\lim_{n \rightarrow \infty} \mathbb{P}_{H_0}[p_{\text{spaCRT}} \leq \alpha] \leq \alpha.$$

Remark 3 (Asymptotic validity of spaCRT). Corollary 1 states the asymptotic validity of spaCRT given the asymptotic validity of dCRT. dCRT is proposed originally assuming the exact knowledge of $\mathcal{L}_n(\mathbf{X} | \mathbf{Z})$, or the so-called Model-X assumption. Under the model-X assumptions, the p -value produced by dCRT procedure is exact, i.e., $\mathbb{P}_{H_0}[p_{\text{dCRT}} \leq \alpha] \leq \alpha$. Therefore, p -value obtained from spaCRT procedure is asymptotically valid under the assumptions of Theorem 1. For asymptotic validity of dCRT with general in-sample fit $\widehat{\mathcal{L}}_n(\mathbf{X} | \mathbf{Z})$, we refer reader to the detailed discussion in Niu et al., 2024.

3.2 Special cases

In the previous section, we established under general conditions the approximation accuracy of the spaCRT (Theorem 1) and its asymptotic equivalence with the dCRT (Theorem 2). We now investigate these conditions in particular cases. To first echo the simulation result in Figure 1, we consider the conditional distribution $\mathbf{X} | \mathbf{Z}$ to be Bernoulli distribution. We need the following assumption to state the formal results.

Assumption 1. $0 < \inf_n \mathbb{E}[(X_{in} - \mathbb{E}[X_{in} | Z_{in}])^2(Y_{in} - \mathbb{E}[Y_{in} | Z_{in}])^2]$.

Lemma 1 (Bernoulli sampling). *Suppose $\mathbf{X} | \mathbf{Z} \sim \text{Ber}(\text{expit}(\theta(\mathbf{Z})))$ and Assumption 1 holds. Furthermore, suppose the following conditions are true:*

$$\frac{1}{n} \sum_{i=1}^n (\mu_{n,y}(Z_{in}) - \widehat{\mu}_{n,y}(Z_{in}))^4 = o_{\mathbb{P}}(1), \quad \frac{1}{n} \sum_{i=1}^n (\theta(Z_{in}) - \widehat{\theta}_{n,x}(Z_{in}))^2 = o_{\mathbb{P}}(1); \quad (17)$$

$$|\widehat{\mu}_{n,y}(Z_{in}) - \mu_{n,y}(Z_{in})| \xrightarrow{a.s.} 0, \quad |\widehat{\theta}_{n,x}(Z_{in}) - \theta(Z_{in})| \xrightarrow{a.s.} 0, \quad \forall i \in [n], n \in \mathbb{N}_+; \quad (18)$$

$$\sup_n \mathbb{E}_{\mathcal{L}_n}[\mathbf{Y}^4] < \infty. \quad (19)$$

Then if condition (13) is true, the conclusion in Theorem 1 holds. Additionally, if the condition (16) is true, the conclusion in Theorem 2 holds.

Remark 4. We can see all these assumptions are very mild conditions. In particular, Assumption 1 is a standard non-degeneracy condition. The conditions (17) and (18) only impose the consistency of estimators without the rate condition requirement. This thus gives much flexibility on estimators $\widehat{\mu}_{n,y}(\cdot)$ and $\widehat{\theta}_{n,x}(\cdot)$. Condition (19) is a standard moment condition. These conditions, together with Assumption 1, are crucial to show the lower bound (12).

Going beyond the Bernoulli sampling, we consider the generalized linear models for both $\mathbf{X} | \mathbf{Z}$ and $\mathbf{Y} | \mathbf{Z}$. The following lemma states the results under this setup.

Lemma 2 (Generalized linear model). *Suppose both $\mathbf{X}|\mathbf{Z}, \mathbf{Y}|\mathbf{Z}$ have generalized linear model distributions with*

$$\mathbb{E}[\mathbf{Y} | \mathbf{Z}] = g(\mathbf{Z}^\top \beta_n), \quad \mathbb{E}[\mathbf{X} | \mathbf{Z}] = h(\mathbf{Z}^\top \alpha_n)$$

where g and h are the inverse link functions and α_n, β_n are coefficients. Consider the estimators $\hat{\alpha}_n, \hat{\beta}_n$ for α_n, β_n . Suppose Assumption 1 holds and the following conditions are true:

support of $\mathbf{Z} \in \mathbb{R}^d$ is compact, i.e., there exists $C_Z, \|\mathbf{Z}\|_\infty \leq C_Z < \infty$; (20)

support of $\mathbf{Y} \in \mathbb{R}$ is compact, i.e., there exists $C_Y, |\mathbf{Y}| \leq C_Y < \infty$; (21)

$$\|\hat{\alpha}_n - \alpha_n\|_1 \xrightarrow{a.s.} 0, \quad \|\hat{\beta}_n - \beta_n\|_1 \xrightarrow{a.s.} 0; \quad (22)$$

$$\sup_n \|\alpha_n\|_1 < \infty, \quad \sup_n \|\beta_n\|_1 < \infty. \quad (23)$$

Then if condition (13) is true, the conclusion in Theorem 1 hold. Additionally, if the condition (16) is true, the conclusion in Theorem 2 holds.

Remark 5. Conditions (20),(22) and (23) are standard conditions that can be satisfied generally. Notice we do not restrict to specific estimators $\hat{\alpha}_n, \hat{\beta}_n$ so even regularized estimators (e.g. lasso or ridge estimators) can satisfy the conditions including the consistency condition (22) easily. Condition (21) is imposed to ensure the residual $a_{in} = Y_{in} - \hat{\mu}_{n,y}(Z_{in})$ to behave nicely.

Even though the theoretical results of this section are only asymptotic, we show in the next section that the finite-sample performance of spaCRT is very similar to that of the dCRT.

4 Numerical simulations

4.1 Simulation setup and methods compared

Even though the spaCRT can accommodate any form of estimators $\hat{\mu}_{n,x}, \hat{\mu}_{n,y}$, we design our simulation to mimic the motivating application of CRISPR screens, where $\mathbf{X} | \mathbf{Z}$ is modeled as a logistic regression model and $\mathbf{Y} | \mathbf{Z}$ is modeled as a negative binomial regression model (Barry et al., 2024; Barry et al., 2021; Gasperini et al., 2019). The latter modeling choice is quite common not just in single-cell CRISPR screen analysis but in single-cell RNA-seq analysis more broadly (Huang et al., 2018; Townes et al., 2019; Svensson, 2020).

Data-generating model: We consider the following data-generating model:

$$\mathbf{Z} \sim N(0, 1); \quad \mathbf{X} | \mathbf{Z} \sim \text{Ber}(\text{expit}(\gamma_0 + \mathbf{Z})); \quad \mathbf{Y} | \mathbf{X}, \mathbf{Z} \sim \text{NB}(\text{exp}(\beta_0 + \rho \mathbf{X} + \mathbf{Z}), r), \quad (24)$$

where $r > 0$ is the *size parameter* controlling the overdispersion of the negative binomial distribution. Here, \mathbf{X} , \mathbf{Y} , and \mathbf{Z} represent the indicator of perturbation presence, gene expression, and a single covariate with a confounding effect, respectively. In this setup, we consider testing for association between a single CRISPR perturbation and a

single gene. This already captures the relevant statistical phenomena. We present the results of analogous high-multiplicity simulations in Appendix E.2, whose results are consistent with those of the simulations presented in the main text. The parameters γ_0 and β_0 control the proportion of cells with perturbations and the mean expression of the gene, respectively, and therefore control the sparsity level of X and Y . The smaller γ_0 and β_0 , the sparser X and Y and the range of these parameters are chosen to roughly match the sparsity level in the real data analyzed in the next section. The parameter ρ controls the strength of the signal, i.e., the dependence of \mathbf{Y} on \mathbf{X} conditional on \mathbf{Z} . Therefore, $\rho = 0$ and $\rho \neq 0$ corresponds to the null and alternative hypotheses, respectively. We adopt the parameter settings displayed in Table 1. Note that the bolded values of -5 for γ_0 and β_0 are the default parameter values. Instead of testing all combinations of these two parameters, we vary one of them while fixing the other to -5. Furthermore, note that our choices of ρ differ based on whether we are carrying out left- or right-sided tests.

γ_0	β_0	ρ (left-sided)	ρ (right-sided)	r	n
-6	-6	-4	0	0.05	5000
-5	-5	-3	0.5	1	
-4	-4	-2	1	10	
-3	-3	-1	1.5		
-2	-2	0	2		

Table 1: Simulation parameter choices.

Methodologies compared: We compare the following four tests, summarized in Table 2. We applied both left- and right-sided variants of each test.

- The **spaCRT** (Algorithm 2), where $\mathbf{X} | \mathbf{Z}$ is fit based on a logistic regression model and $\mathbf{Y} | \mathbf{Z}$ is fit based on a negative binomial regression model. The size parameter r is estimated by applying the method of moments to the residuals of the Poisson regression of Y on Z (Barry et al., 2021; Barry et al., 2024). This method (called “precomputed” in Table 2) is fast but less accurate than maximum likelihood estimation, but is sufficient for the spaCRT, which does not require accurate estimation of the size parameter. We use the `uniroot` function in R to solve the equation saddlepoint equation. When the solution is not found or the resulting p -value p_{spaCRT} is not in the range $[0, 1]$, we use the p -value based on the GCM test as a backup (see below). **We found the failure to solve the saddlepoint equation quite rare, occurring in at most 1.3% of replications across all simulation settings.**
- The **dCRT** (Algorithm 1), with the same fitting procedures as the spaCRT and $M = 10,000$.
- The **GCM test** (Shah and Peters, 2020), which is based on the asymptotically normal test statistic

$$T_n^{\text{GCM}} \equiv \frac{T_n^{\text{dCRT}}(X, Y, Z)}{\widehat{S}_n}, \quad \widehat{S}_n^2 \equiv \frac{1}{n} \sum_{i=1}^n R_{in}^2 - \left(\frac{1}{n} \sum_{i=1}^n R_{in} \right)^2,$$

where $T_n^{\text{dCRT}}(X, Y, Z)$ is defined as in (3) and

$$R_{in} \equiv (X_{in} - \hat{\mu}_{n,x}(Z_{in}))(Y_{in} - \hat{\mu}_{n,y}(Z_{in})).$$

We use the same fitting procedures for the GCM test as for spaCRT and dCRT.

- The **negative binomial regression score test** (implemented via the `glm.nb()` function in the `MASS` package). This function computes the maximum likelihood estimate of the size parameter iteratively, which is slower than the precomputed approach but more accurate. We choose this approach since the score test relies more heavily on the accuracy of the size parameter estimate.

Test	Dispersion estimation	Resampling required	Normality-based
GCM	Precomputed	No	Yes
Score test	Iterative	No	Yes
dCRT	Precomputed	Yes	No
spaCRT	Precomputed	No	No

Table 2: Summary table for testing methods compared.

All simulations are repeated 50,000 times for accurate Type-I error estimation for small p -value thresholds.

4.2 Simulation results

Here, we present a representative selection of simulation results (Figure 2). These results correspond to $r = 0.05$ and $\beta_0 = -5$, and all tests are applied at nominal level $\alpha = 0.01$. Additional figures with more detailed results are provided in Appendix E.1. We find from Figure 2a, which displays p -value distributions under the null hypothesis, that the spaCRT and dCRT tests have similar p -value distributions, both of which are close to uniform. Meanwhile, the GCM test behaves too liberally for left-sided tests and too conservatively for right-sided tests, while the score test behaves too conservatively for left-sided tests and too liberally for right-sided tests. These trends are reflected in the Type-I error rates and powers in Figure 2b,c. We remark that the spaCRT and dCRT tests control Type-I error for all settings of γ_0 , though both tests tend to become conservative as X becomes sparser. Furthermore, the spaCRT and dCRT are the most powerful tests among those that have Type-I error control for every parameter setting.

Next, we remark on how the methods' performance is impacted by the problem parameters γ_0 , β_0 , and r . As either X or Y become less sparse (i.e., as γ_0 or β_0 increase), the p -value distributions, Type-I error rates, and powers for the GCM and score tests improve. This is to be expected, as the test statistics converge more quickly towards the standard normal distribution when the quantities being averaged are less sparse. We also find that larger size parameters r lead to better behavior for the GCM and score tests. This is also to be expected, because smaller size parameters make the negative binomial distribution more skewed, and therefore it requires more samples for the test statistics to converge to the normal distribution. Furthermore, smaller size parameters are more difficult to estimate accurately due to the increased variance in

the gene expression Y , which impacts the score test. On the other hand, the dCRT and spaCRT behave much more stably across different sparsity levels of X and Y and different values of the size parameter r , since these methods do not rely on the central limit theorem.

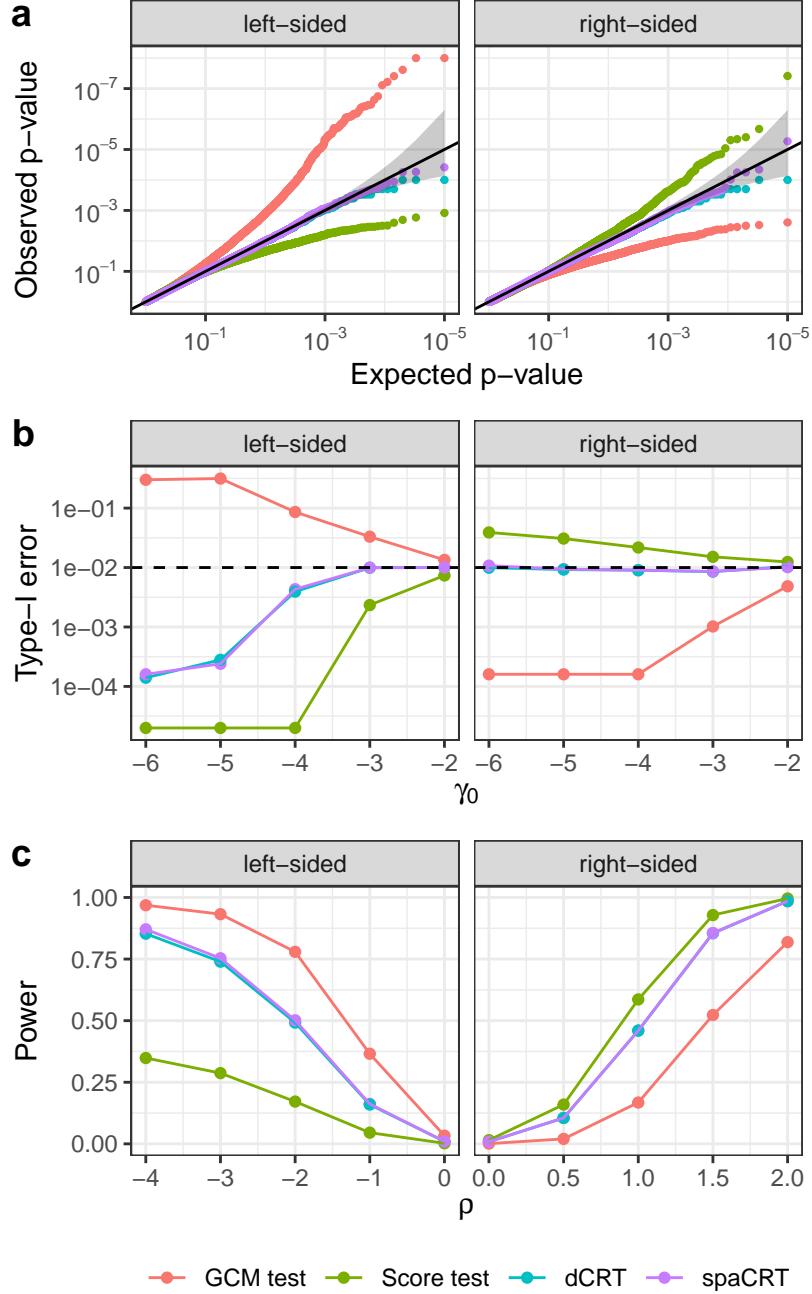


Figure 2: Summary of numerical simulation results for size parameter $r = 0.05$. (a) QQ-plots of the p -values obtained under the null hypothesis for $(\gamma_0, \beta_0) = (-3, -5)$. (b) Type-I error rates for $\beta_0 = -5$ as a function of the sparsity of X (γ_0), when testing at level $\alpha = 0.01$. (c) Power for $(\gamma_0, \beta_0) = (-3, -5)$ as a function of the signal strength (ρ), when testing at level $\alpha = 0.01$.

Moreover, Figure 3 displays the computing times for the different methods in the settings considered in Figure 2. We see that the spaCRT and GCM test are roughly tied for fastest, the score test is roughly half an order of magnitude slower than these two, while the dCRT is more than an order of magnitude slower. Finally, scatter plots in Figure 4 confirm the alignment between p -values obtained from dCRT and spaCRT, which backs up the theoretical results proved in section 3. We refer additional scatter plots and how these scatter plots are generated to section E.1.

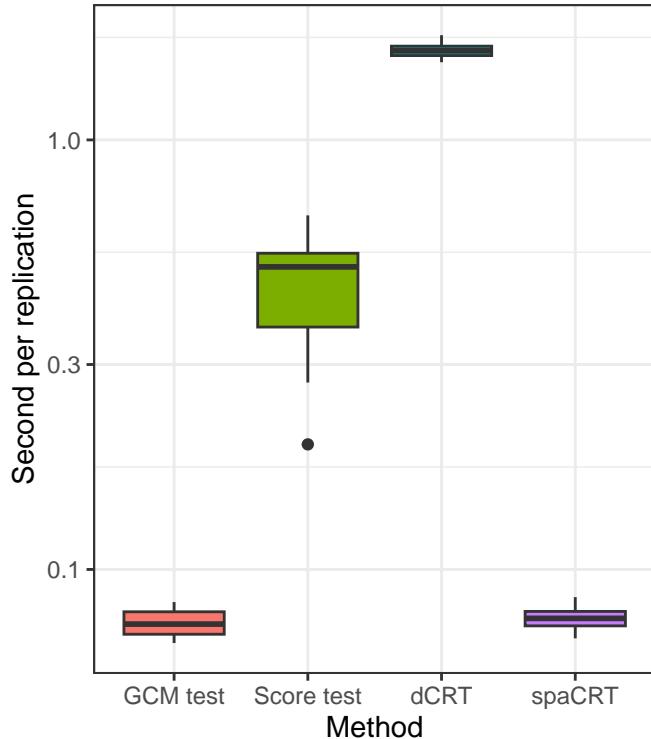


Figure 3: Computing times for numerical simulation with $r = 0.05$ and $\beta_0 = -5$.

5 Real data analysis

In this section, we compare the performance of the spaCRT to those of alternative methods on the analysis of the Gasperini et al. (2019) single-cell CRISPR screen dataset.

5.1 Overview of the data

The Gasperini data contain expression measurements on 13,135 genes and CRISPR perturbations targeting 6,105 regulatory elements in $n = 207,324$ cells. They also contain CRISPR perturbations intended as negative and positive controls. In particular, the data contain 51 non-targeting CRISPR perturbations, which do not target any regulatory element and therefore should have no effect on the expressions of any genes. Furthermore, the data contain 754 CRISPR perturbations targeting genes, rather than

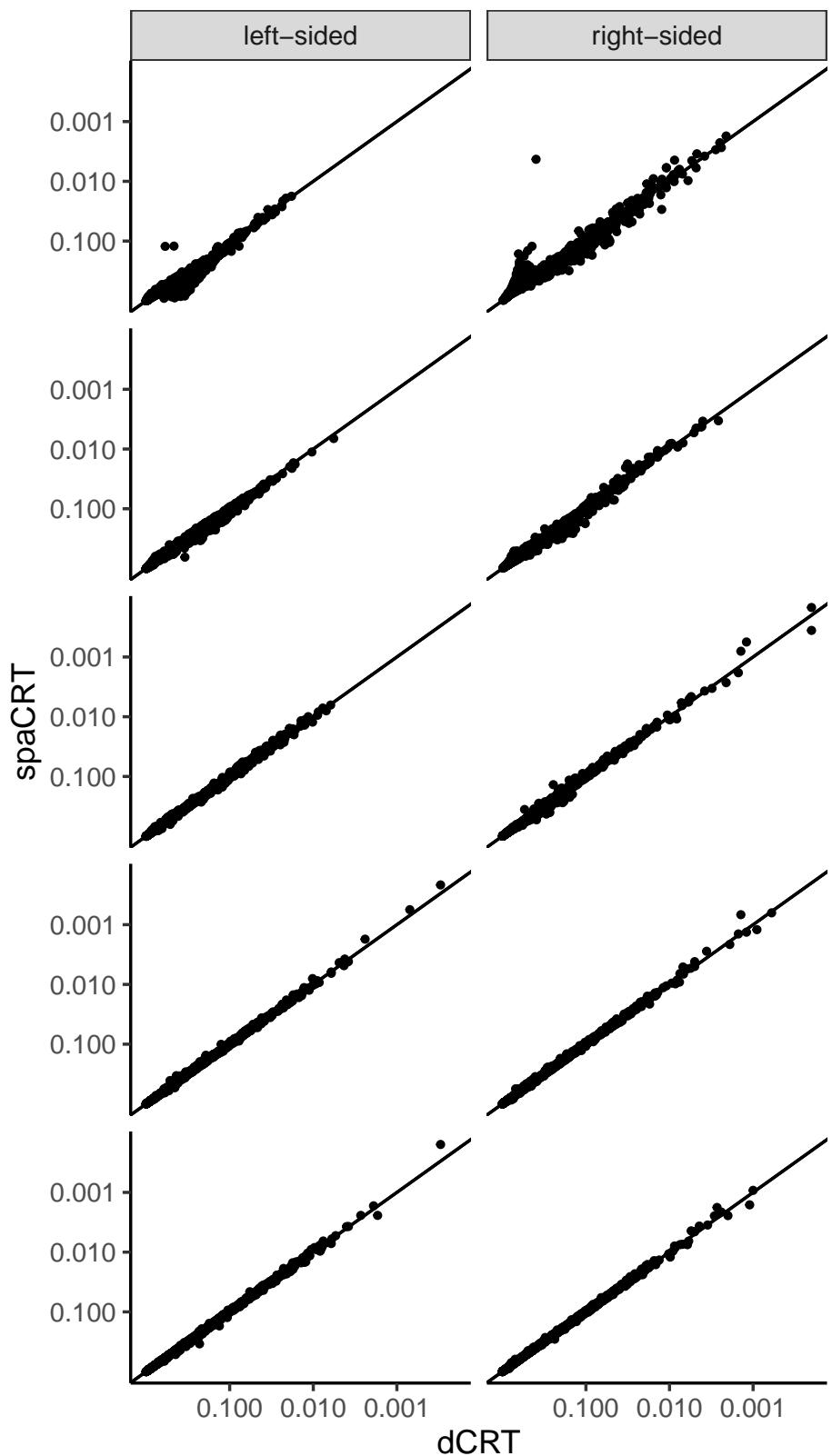


Figure 4: Scatter plots for the p -values of the left-sided and right-sided tests when varying $\gamma_0 \in \{-6, -5, -4, -3, -2\}$ and fixing $\beta_0 = -5$, with $\theta = 0.05$.

regulatory elements. These serve as positive controls, because they are known a priori to have effects on the expressions of the genes they target. Finally, the data contain measurements on six covariates, including four count-based covariates related to library size, one binary covariate indicating the experimental batch, and one continuous covariate indicating the proportion of reads mapping to mitochondrial genes in each cell.

5.2 Analyses conducted

Hypotheses tested. In order to assess the Type-I error and power of the methods compared, we will use CRISPR perturbations intended as negative and positive controls, respectively. In particular, for Type-I error analysis, we test for association between each of the 51 negative control perturbations and each of 3,000 randomly sampled genes, for a total of $51 \times 3,000 = 153,000$ tests. We subsample the genes to reduce the computational burden of the analysis. To assess the power of each method, we test for association between each of the 754 positive control perturbations targeting genes and the gene they target, for a total of 754 tests.

Methods compared. We compare essentially the same methods as in the numerical simulations (recall Section 4.1). The only difference is that we replace the dCRT with a faster variant implemented in the `sceptre` package, in order to make the analysis computationally feasible. The `sceptre` implementation of the dCRT fits a parametric curve to the resampling distribution of the test statistic based on a smaller number of resamples (a heuristic acceleration that is not theoretically justified). Furthermore, it is implemented in C++ for speed, unlike the other methods we consider, which are implemented in R. We apply left- and right-sided variants of each test on the negative control perturbation-gene pairs. For the positive control pairs, we apply only left-sided tests, since we are testing for a perturbation-induced decrease in gene expression.

5.3 Results

Type-I error. Figure 5 displays QQ plots of the negative control p -values obtained from all four methods. The two tests relying on asymptotic normality, the GCM and score tests, exhibit severe p -value inflation for left- and right-sided tests, respectively. This finding is consistent with our simulation results (Figure 2). On the other hand, the spaCRT and `sceptre` tests control Type-I error well for both left- and right-sided tests. **We also report the number of false discoveries on the negative control pairs in Appendix F.2; the message from these results are consistent with that of the single testing results.**

Next, we investigate the impact of the problem sparsity on calibration. Following (Barry et al., 2024), we measure sparsity in terms of the *effective sample size* $\sum_{i=1}^n \mathbb{1}(X_i Y_i > 0)$, which measures the number of cells with a given perturbation and nonzero expression of a given gene. Table 3 displays the distribution of effective sample sizes across the negative control perturbation-gene pairs tested, showing that the effective samples sizes are vastly smaller than the number of cells, $n = 207,324$. Furthermore, Figure 24 stratifies the QQ plots for each method by effective sample size,

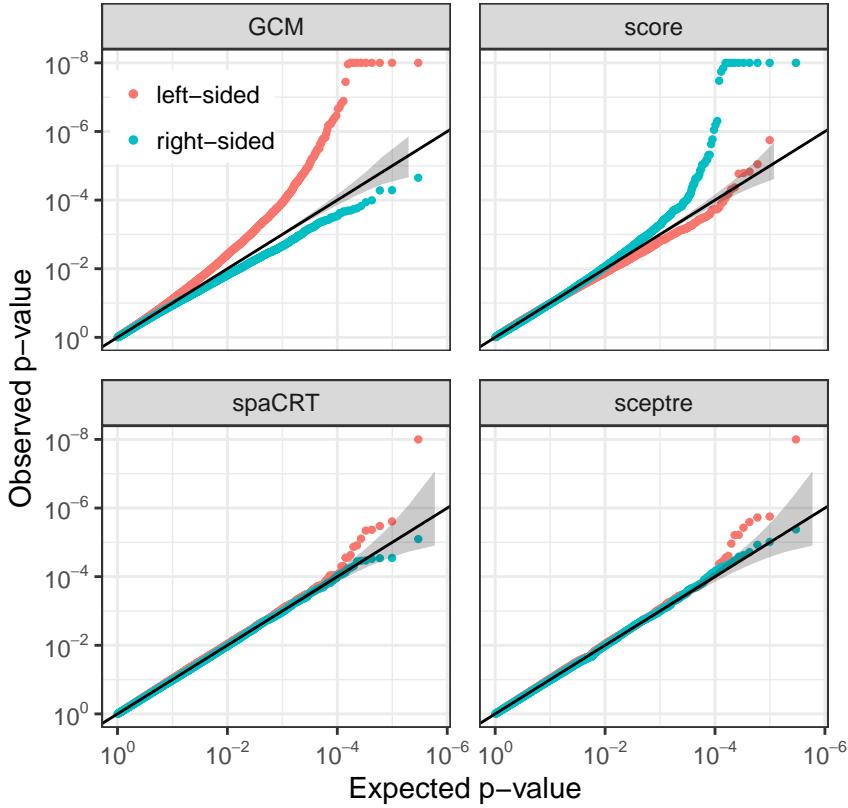


Figure 5: Left- and right-sided p -values for negative control perturbation-gene pairs on the Gasperini data.

focusing on those pairs with effective sample size of at most 100. As expected based on our simulation study, we find more severe miscalibration for pairs with lower effective sample sizes, especially for the GCM and score tests, and to a lesser extent for `sceptre` and the spaCRT. We carried out a similar analysis, stratifying the pairs based on the estimated size parameter (Figure 25). In line with our simulation results, we find that the GCM and score tests exhibit more miscalibration for smaller size parameters.

	Min.	1st Qu.	Median	3rd Qu.	Max.
Effective sample size	0	53	204	504	2044

Table 3: Effective sample size in subsampled dataset.

Power. Next, we compare the power of the four methods based on their left-sided p -values on the 754 positive control perturbation-gene pairs (Figure 6). The signal is quite strong in these positive control pairs, as evidenced by small p -values for all four methods. **We remark that the spaCRT overcomes the discreteness in the p -values returned by resampling-based methods such as the dCRT, delivering very small p -values in the presence of strong signals.** Given the scale of the p -values, we refrain from making definitive conclusions about the relative power of the methods, but remark only that the spaCRT appears at least as powerful as the alternative methods considered.

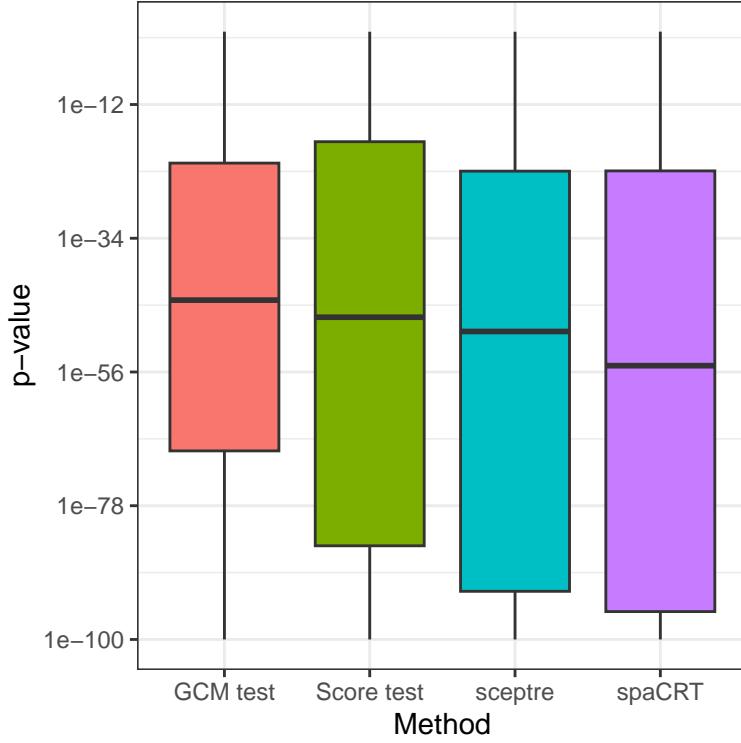


Figure 6: Left-sided p -values computed on the 754 positive control perturbation-gene pairs in the Gasperini et al. (2019) data.

Computation. The excellent statistical properties of the spaCRT do not come at the cost of computational efficiency. Since the `sceptre` software is highly optimized, while the other methods are not, we benchmark our dCRT implementation (used in the numerical simulations) instead of `sceptre`'s for computational efficiency. We use $M = 100,000$ resamples for the dCRT, given the high multiplicity of the problem (recall Section 1.2). To assess running time, we paired two randomly sampled genes with each of the 51 non-targeting perturbations, for a total of 102 perturbation-gene pairs. We find that the spaCRT is roughly as fast as the GCM test, about five times faster than the score test, and about 250 times faster than the dCRT.

Table 4: Computation time per perturbation-gene pair on the Gasperini data. Times are reported in seconds.

Method	Mean	Std dev
GCM test	4.0	1.9
dCRT	1002.1	279.5
spaCRT	4.0	1.9
Score test	19.9	9.3

6 Discussion

In this paper, we introduce the spaCRT, a new conditional independence test enjoying several desirable properties: (1) It is completely resampling-free, which makes it very computationally efficient. (2) It is asymptotically equivalent to the doubly robust dCRT, so it has Type-I error control without requiring the model-X assumption. (3) It has excellent Type-I error control and power in both numerical simulations and real data analysis. The spaCRT is particularly well-suited to single-cell CRISPR screen data analysis, where it can significantly accelerate the state-of-the-art `sceptre` software without sacrificing statistical performance.

Despite the attractive properties of the spaCRT, the current work still has several limitations. First, there remains a gap between our theoretical guarantees and the practical performance of the spaCRT and dCRT. We have shown that both of these tests have Type-I error control asymptotically, but we have not theoretically justified why these tests perform so well in finite samples, compared with asymptotic tests like the GCM and score tests. Second, we have focused on approximating the dCRT in this paper, but the conditional randomization test framework is applicable to general test statistics. It would be interesting to see how the saddlepoint approximation can be extended to other test statistics.

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A Probability theory preliminaries

A.1 Single probability space embedding

To better state and understand the conditional convergence result, the following lemma helps to embed all the random variables into one big probability space.

Lemma 3 (Embedding into a single probability space, Lemma 14 in Niu et al., 2024). *Consider a sequence of probability spaces $\{(\mathbb{P}_n, \Omega_n, \mathcal{G}_n), n \geq 1\}$. For each n , let $\{W_{i,n}\}_{i \geq 1}$ be a collection of integrable random variables defined on $(\mathbb{P}_n, \Omega_n, \mathcal{G}_n)$ and let $\mathcal{F}_n \subseteq \mathcal{G}_n$ be a σ -algebra. Then there exists a single probability space $(\tilde{\mathbb{P}}, \tilde{\Omega}, \tilde{\mathcal{G}})$, random variables $\{\tilde{W}_{i,n}\}_{i,n \geq 1}$ on $(\tilde{\mathbb{P}}, \tilde{\Omega}, \tilde{\mathcal{G}})$, and σ -fields $\tilde{\mathcal{F}}_n \subseteq \tilde{\mathcal{G}}$ for $n \geq 1$, such that for each n , the joint distribution of $(\{W_{i,n}\}_{i \geq 1}, \{\mathbb{E}[W_{i,n} | \mathcal{F}_n]\}_{i \geq 1})$ on $(\mathbb{P}_n, \Omega_n, \mathcal{G}_n)$ coincides with that of $(\{\tilde{W}_{i,n}\}_{i \geq 1}, \{\mathbb{E}[\tilde{W}_{i,n} | \tilde{\mathcal{F}}_n]\}_{i \geq 1})$ on $(\tilde{\mathbb{P}}, \tilde{\Omega}, \tilde{\mathcal{G}})$.*

With the above Lemma, we are safe to state any almost sure statement which can be interpreted within one probability space.

A.2 Some facts about natural exponential family

Consider the NEF with probability density function

$$f(x|\theta) = h(x) \exp(\theta x - A(\theta)).$$

Then there is one-to-one correspondence between the moments of the random variable from NEF and the derivative of the log-partition function $A(\theta)$. We summarise the relationship in the following Lemma.

Lemma 4 (Chapter 1.2 in Efron, 2022). *Suppose $X \sim f(x|\theta)$ then the following identities hold:*

1. $\mathbb{E}[X] = A'(\theta);$
2. $\mathbb{E}[X^2] - (\mathbb{E}[X])^2 = A''(\theta);$
3. $\mathbb{E}[(X - \mathbb{E}[X])^3] = A^{(3)}(\theta);$
4. $\mathbb{E}[(X - \mathbb{E}[X])^4] - 3(\mathbb{E}[(X - \mathbb{E}[X])^2])^2 = A^{(4)}(\theta).$

B Preliminaries for saddlepoint approximation

Let W be a random variable on $(\Omega, \mathcal{F}, \mathbb{P})$ and let $\mathcal{G} \subseteq \mathcal{F}$ be a σ -algebra. Consider the following definitions.

Definition 1 (CSE distribution). *Consider a random variable $\theta \in \mathcal{G}$ such that $\theta \geq 0$ almost surely and a constant $\beta > 0$. We say $W|\mathcal{G}$ is conditionally sub-exponential (CSE) with parameters (θ, β) if, almost surely,*

$$\mathbb{P}[|W| \geq t | \mathcal{G}] \leq \theta \exp(-\beta t), \text{ for all } t > 0.$$

We denote this property via $W|\mathcal{G} \sim \text{CSE}(\theta, \beta)$.

Definition 2 (CCS distribution). Consider a random variable $\nu \in \mathcal{G}$ such that $\nu \geq 0$ almost surely. We say $W|\mathcal{G}$ is conditionally compactly supported (CCS) on $[-\nu, \nu]$ if

$$W \in [-\nu, \nu] \quad \text{almost surely.}$$

We denote this property via $W|\mathcal{G} \sim CCS(\nu)$.

Consider a triangular array $\{W_{in}\}_{1 \leq i \leq n, n \geq 1}$ and σ -algebra \mathcal{F}_n , so that $\mathbb{E}[W_{in}|\mathcal{F}_n] = 0$ for each (i, n) , and $\{W_{in}\}_{1 \leq i \leq n}$ are independent conditionally on \mathcal{F}_n for each n . Now, we impose assumptions on the triangular array $\{W_{in}\}_{1 \leq i \leq n, n \geq 1}$ in terms of Definition 1-2. We assume throughout this section that Assumption 2 or Assumption 3 holds.

Assumption 2 (CSE condition). There exist $\theta_n \in \mathcal{F}_n$ and $\beta > 0$ such that

$$W_{in}|\mathcal{F}_n \sim CSE(\theta_n, \beta) \text{ for all } i, n, \quad \theta_n < \infty \text{ almost surely,} \quad \theta_n = O_{\mathbb{P}}(1). \quad (25)$$

Assumption 3 (CCS condition). There exist $\nu_{in} \in \mathcal{F}_n$ such that

$$W_{in}|\mathcal{F}_n \sim CCS(\nu_{in}), \quad \nu_{in} < \infty \text{ almost surely,} \quad \text{and} \quad \frac{1}{n} \sum_{i=1}^n \nu_{in}^4 = O_{\mathbb{P}}(1). \quad (26)$$

Given the sequence $x_n \in \mathcal{F}_n$, we would like to approximate tail probabilities for the average $W_n \equiv \frac{1}{n} \sum_{i=1}^n W_{in}$:

$$\mathbb{P}[W_n \geq x_n|\mathcal{F}_n]$$

We will approximate this tail probability via the saddlepoint approximation. This requires the existence of the conditional cumulant generating function (CGF):

$$K_n(s|\mathcal{F}_n) \equiv \frac{1}{n} \sum_{i=1}^n K_{in}(s|\mathcal{F}_n), \quad K_{in}(s|\mathcal{F}_n) \equiv \log \mathbb{E}[\exp(sW_{in})|\mathcal{F}_n].$$

Here $K_{in}(\cdot | \mathcal{F}_n)$ is the conditional CGF of W_{in} . The very first step in saddlepoint approximation is to find the tilting parameter \hat{s}_n solving the *saddlepoint equation*

$$K'_n(s|\mathcal{F}_n) = x_n. \quad (27)$$

Then the validity of the saddlepoint approximation is formalized in the following two lemmas.

Lemma 5 (Lemma 1 in Niu, Ray Choudhury, and Katsevich, 2024). Suppose Assumption 2 or Assumption 3 holds. Then, there exists a probability-one event \mathcal{A} and an $\varepsilon > 0$ such that, on \mathcal{A} ,

$$K_{in}(s) < \infty \quad \text{for any } s \in (-\varepsilon, \varepsilon) \text{ and for all } i \leq n, n \geq 1. \quad (28)$$

In particular, when Assumption 2 holds, $\varepsilon = \beta/8$ and when Assumption 3 holds, $\varepsilon = 1/8$.

Lemma 6 (Theorem 1 in Niu, Ray Choudhury, and Katsevich, 2024). *Let W_{in} be a triangular array of random variables that are mean-zero and independent for each n , conditionally on \mathcal{F}_n . Suppose either Assumption 2 or Assumption 3 holds, and that*

$$\frac{1}{n} \sum_{i=1}^n \mathbb{E}[W_{in}^2 | \mathcal{F}_n] = \Omega_{\mathbb{P}}(1). \quad (29)$$

Let $x_n \in \mathcal{F}_n$ be a sequence with $x_n \xrightarrow{\mathbb{P}} 0$ and $\varepsilon > 0$ is defined as in Lemma 5. Then, the saddlepoint equation (27) has a unique and finite solution $\hat{s}_n \in [-\varepsilon/2, \varepsilon/2]$ with probability approaching 1 as $n \rightarrow \infty$. If we define $\lambda_n \equiv \hat{s}_n \sqrt{n K_n''(\hat{s}_n | \mathcal{F}_n)}$ and

$$r_n \equiv \begin{cases} \text{sgn}(\hat{s}_n) \sqrt{2n(\hat{s}_n x_n - K_n(\hat{s}_n | \mathcal{F}_n))} & \text{if } \hat{s}_n x_n - K_n(\hat{s}_n | \mathcal{F}_n) \geq 0; \\ \text{sgn}(\hat{s}_n) & \text{otherwise,} \end{cases}$$

then

$$\mathbb{P} \left[\frac{1}{n} \sum_{i=1}^n W_{in} \geq x_n \mid \mathcal{F}_n \right] = \left(1 - \Phi(r_n) + \phi(r_n) \left\{ \frac{1}{\lambda_n} - \frac{1}{r_n} \right\} \right) (1 + o_{\mathbb{P}}(1)).$$

and

$$\mathbb{P} \left[1 - \Phi(r_n) + \phi(r_n) \left\{ \frac{1}{\lambda_n} - \frac{1}{r_n} \right\} > 0 \right] \rightarrow 1 \text{ as } n \rightarrow \infty.$$

C Some useful lemmas and proofs

Lemma 7 (Lemma 3 in Niu et al., 2024). *Consider two hypothesis tests based on the same test statistic $T_n(X, Y, Z)$ but different critical values:*

$$\phi_n^1(X, Y, Z) \equiv \mathbb{1}(T_n(X, Y, Z) > C_n(X, Y, Z)); \quad \phi_n^2(X, Y, Z) \equiv \mathbb{1}(T_n(X, Y, Z) > z_{1-\alpha}).$$

If the critical value of the first converges in probability to that of the second:

$$C_n(X, Y, Z) \xrightarrow{\mathbb{P}} z_{1-\alpha}$$

and the test statistic does not accumulate near the limiting critical value:

$$\lim_{\delta \rightarrow 0} \limsup_{n \rightarrow \infty} \mathbb{P}_{\mathcal{L}_n}[|T_n(X, Y, Z) - z_{1-\alpha}| \leq \delta] = 0, \quad (30)$$

then the two tests are asymptotically equivalent:

$$\lim_{n \rightarrow \infty} \mathbb{P}_{\mathcal{L}_n}[\phi_n^1(X, Y, Z) = \phi_n^2(X, Y, Z)] = 1.$$

Regularity condition: there exists $\delta > 0$ such that for a sequence of laws \mathcal{L}_n and its estimate $\widehat{\mathcal{L}}_n$, the following assumptions hold:

$$(\widehat{S}_n^{\text{dCRT}})^2 \equiv \frac{1}{n} \sum_{i=1}^n \text{Var}_{\widehat{\mathcal{L}}_n}[X_{in} | Z_{in}] (Y_{in} - \widehat{\mu}_{n,y}(Z_{in}))^2 = \Omega_{\mathbb{P}}(1); \quad (31)$$

$$\frac{1}{n^{1+\delta/2}} \sum_{i=1}^n |Y_{in} - \widehat{\mu}_{n,y}(Z_{in})|^{2+\delta} \mathbb{E}_{\widehat{\mathcal{L}}_n}[|\widetilde{X}_{in} - \widehat{\mu}_{n,x}(Z_{in})|^{2+\delta} \mid X, Z] = o_{\mathbb{P}}(1); \quad (32)$$

$$\text{Var}_{\widehat{\mathcal{L}}_n}[X_{in} | Z_{in}], (Y_{in} - \widehat{\mu}_{n,y}(Z_{in}))^2, (Y_{in} - \mu_{n,y}(Z_{in}))^2 < \infty \text{ almost surely.} \quad (33)$$

Lemma 8 (Theorem 9 in Niu et al., 2024). *Let \mathcal{L}_n be a sequence of laws and $\widehat{\mathcal{L}}_n$ be a sequence of estimates. Suppose there exists a sequence of laws \mathcal{L}_n satisfying all the assumptions in **Regularity condition**. Then, the quantile of*

$$T_n^{\text{ndCRT}}(\widetilde{X}, X, Y, Z) \equiv \frac{T_n^{\text{dCRT}}(\widetilde{X}, X, Y, Z)}{\widehat{S}_n^{\text{dCRT}}} \quad (34)$$

converges to the quantile of the standard normal distribution pointwisely in probability, i.e., for any $p \in (0, 1)$,

$$\mathbb{Q}_p \left[n^{1/2} T_n^{\text{ndCRT}}(\widetilde{X}, X, Y, Z) | X, Y, Z \right] \xrightarrow{\mathbb{P}} z_p.$$

Lemma 9 (Corollary 6 in Niu et al., 2024). *Let X_{in} be a triangular array of random variables, such that X_{in} are independent for each n . If for some $\delta > 0$ we have*

$$\frac{1}{n^{1+\delta}} \sum_{i=1}^n \mathbb{E}[|X_{in}|^{1+\delta}] \rightarrow 0, \quad (35)$$

then

$$\frac{1}{n} \sum_{i=1}^n (X_{in} - \mathbb{E}[X_{in}]) \xrightarrow{\mathbb{P}} 0.$$

The condition (35) is satisfied when

$$\sup_{1 \leq i \leq n} \mathbb{E}[|X_{in}|^{1+\delta}] = o(n^\delta).$$

Lemma 10 (Dominance of higher moment). *For any $1 < p < q < \infty$, the following inequality is true almost surely:*

$$\frac{1}{n} \sum_{i=1}^n \mathbb{E}[|X_{in}|^p | \mathcal{F}_n] \leq \left(\frac{1}{n} \sum_{i=1}^n \mathbb{E}[|X_{in}|^q | \mathcal{F}_n] \right)^{p/q}.$$

Lemma 11 (Conditional Hölder inequality, Swanson, 2019, Theorem 6.60). *Let W_1 and W_2 be random variables and let \mathcal{F} be a σ -algebra. If for some $q_1, q_2 \in (1, \infty)$ with $\frac{1}{q_1} + \frac{1}{q_2} = 1$ we have $\mathbb{E}[|W_1|^{q_1}], \mathbb{E}[|W_2|^{q_2}] < \infty$, then*

$$\mathbb{E}[|W_1 W_2| | \mathcal{F}] \leq (\mathbb{E}[|W_1|^{q_1} | \mathcal{F}])^{1/q_1} (\mathbb{E}[|W_2|^{q_2} | \mathcal{F}])^{1/q_2} \quad \text{almost surely.}$$

Lemma 12 (Conditional Jensen inequality, Davidson, 1994, Theorem 10.18). *Let W be a random variable and let ϕ be a convex function, such that W and $\phi(W)$ are integrable. For any σ -algebra \mathcal{F} , we have the inequality*

$$\phi(\mathbb{E}[W | \mathcal{F}]) \leq \mathbb{E}[\phi(W) | \mathcal{F}] \quad \text{almost surely.}$$

C.1 Proof of Lemma 10

Proof of Lemma 10. By Lemma 11, we have

$$\begin{aligned} \frac{1}{n} \sum_{i=1}^n \mathbb{E}[|X_{in}|^p | \mathcal{F}_n] &\leq \frac{1}{n} \left(\sum_{i=1}^n (\mathbb{E}[|X_{in}|^p | \mathcal{F}_n])^{q/p} \right)^{p/q} n^{1-p/q} \\ &= \left(\frac{1}{n} \sum_{i=1}^n (\mathbb{E}[|X_{in}|^p | \mathcal{F}_n])^{q/p} \right)^{p/q}. \end{aligned}$$

We use Jensen's inequality, Lemma 12, to obtain

$$\frac{1}{n} \sum_{i=1}^n \mathbb{E}[|X_{in}|^p | \mathcal{F}_n] \leq \left(\frac{1}{n} \sum_{i=1}^n \mathbb{E}[|X_{in}|^q | \mathcal{F}_n] \right)^{p/q}.$$

□

D Proof of results in section 3

D.1 Proof of Theorem 1

We have conditional CGF

$$K_{in}(s | \mathcal{F}_n) = A(\hat{\theta}_{n,x}(Z_{in}) + a_{in}s) - A(\hat{\theta}_{n,x}(Z_{in})) - a_{in}sA'(\hat{\theta}_{n,x}(Z_{in})). \quad (36)$$

We will apply Lemma 6 and thus verify the conditions in the lemma. We first verify the variance condition (29).

Verification of (29): Compute $K''_{in}(s | \mathcal{F}_n) = a_{in}^2 A''(\hat{\theta}_{n,x}(Z_{in}) + a_{in}s)$. Then it suffices to guarantee

$$\frac{1}{n} \sum_{i=1}^n \mathbb{E}[W_{in}^2 | \mathcal{F}_n] = \frac{1}{n} \sum_{i=1}^n K''_{in}(0 | \mathcal{F}_n) = \frac{1}{n} \sum_{i=1}^n a_{in}^2 A''(\hat{\theta}_{n,x}(Z_{in})) = \Omega_{\mathbb{P}}(1).$$

Next we verify assumption 2 and condition (CCS) respectively.

Verification of Assumption 2 with condition (CSE) and (11): We denote the conditional upper tail probability and lower probability respectively as

$$L_{X,\mathcal{F}_n}(a) \equiv \mathbb{P}[X \leq a | \mathcal{F}_n], \quad U_{X,\mathcal{F}_n}(a) \equiv \mathbb{P}[X \geq a | \mathcal{F}_n].$$

Then by the definition of CSE distribution (Definition 1), we can compute

$$\begin{aligned} \mathbb{P}[W_{in} \geq t | \mathcal{F}_n] &= \mathbb{P}[a_{in}(\tilde{X}_{in} - A'(\hat{\theta}_{n,x}(Z_{in}))) \geq t | \mathcal{F}_n] \\ &= \mathbb{1}(a_{in} > 0)U_{\tilde{X}_{in},\mathcal{F}_n}\left(\frac{t}{a_{in}} + A'(\hat{\theta}_{n,x}(Z_{in}))\right) + \mathbb{1}(a_{in} < 0)L_{\tilde{X}_{in},\mathcal{F}_n}\left(\frac{t}{a_{in}} + A'(\hat{\theta}_{n,x}(Z_{in}))\right) \end{aligned}$$

Then by the definition of natural exponential family, we can write

$$\begin{aligned}
& \mathbb{1}(a_{in} > 0) U_{\tilde{X}_{in}, \mathcal{F}_n} \left(\frac{t}{a_{in}} + A'(\hat{\theta}_{n,x}(Z_{in})) \right) \\
&= \mathbb{1}(a_{in} > 0) \int_{t/a_{in} + A'(\hat{\theta}_{n,x}(Z_{in}))}^{\infty} \exp(\hat{\theta}_{n,x}(Z_{in})x - A(\hat{\theta}_{n,x}(Z_{in}))) h(x) dx \\
&= \mathbb{1}(a_{in} > 0) \int_{t/a_{in} + A'(\hat{\theta}_{n,x}(Z_{in}))}^{\infty} \exp(\hat{\theta}_{n,x}(Z_{in})x + a_{in}x - a_{in}x - A(\hat{\theta}_{n,x}(Z_{in}))) h(x) dx \\
&\leq \mathbb{1}(a_{in} > 0) \int_{t/a_{in} + A'(\hat{\theta}_{n,x}(Z_{in}))}^{\infty} \exp((\hat{\theta}_{n,x}(Z_{in}) + a_{in})x - A(\hat{\theta}_{n,x}(Z_{in}))) h(x) dx \\
&\quad \times \exp(-t - a_{in}A'(\hat{\theta}_{n,x}(Z_{in}))) \\
&\leq \mathbb{1}(a_{in} > 0) \int_{t/a_{in} + A'(\hat{\theta}_{n,x}(Z_{in}))}^{\infty} \exp((\hat{\theta}_{n,x}(Z_{in}) + a_{in})x - A(a_{in} + \hat{\theta}_{n,x}(Z_{in}))) h(x) dx \\
&\quad \times \exp(A(a_{in} + \hat{\theta}_{n,x}(Z_{in})) - A(\hat{\theta}_{n,x}(Z_{in}))) \exp(-t - a_{in}A'(\hat{\theta}_{n,x}(Z_{in}))) \\
&\leq \mathbb{1}(a_{in} > 0) \exp(A(\hat{\theta}_{n,x}(Z_{in}) + a_{in}) - A(\hat{\theta}_{n,x}(Z_{in})) - a_{in}A'(\hat{\theta}_{n,x}(Z_{in}))) \exp(-t) \\
&\leq \mathbb{1}(a_{in} > 0) \exp(|A(\hat{\theta}_{n,x}(Z_{in}) + a_{in})| + |A(\hat{\theta}_{n,x}(Z_{in}))| + |a_{in}| |A'(\hat{\theta}_{n,x}(Z_{in}))|) \exp(-t)
\end{aligned}$$

Similarly, we can derive the upper bound for the lower tail Probability:

$$\begin{aligned}
& \mathbb{1}(a_{in} < 0) L_{\tilde{X}_{in}, \mathcal{F}_n} \left(\frac{t}{a_{in}} + A'(\hat{\theta}_{n,x}(Z_{in})) \right) \\
&= \mathbb{1}(a_{in} < 0) \int_{-\infty}^{t/a_{in} + A'(\hat{\theta}_{n,x}(Z_{in}))} \exp(\hat{\theta}_{n,x}(Z_{in})x - A(\hat{\theta}_{n,x}(Z_{in}))) h(x) dx \\
&= \mathbb{1}(a_{in} < 0) \int_{-\infty}^{t/a_{in} + A'(\hat{\theta}_{n,x}(Z_{in}))} \exp(\hat{\theta}_{n,x}(Z_{in})x + a_{in}x - a_{in}x - A(\hat{\theta}_{n,x}(Z_{in}))) h(x) dx \\
&\leq \mathbb{1}(a_{in} < 0) \exp(A(\hat{\theta}_{n,x}(Z_{in}) + a_{in}) - A(\hat{\theta}_{n,x}(Z_{in})) - a_{in}A'(\hat{\theta}_{n,x}(Z_{in}))) \exp(-t) \\
&\leq \mathbb{1}(a_{in} < 0) \exp(|A(\hat{\theta}_{n,x}(Z_{in}) + a_{in})| + |A(\hat{\theta}_{n,x}(Z_{in}))| + |a_{in}| |A'(\hat{\theta}_{n,x}(Z_{in}))|) \exp(-t).
\end{aligned}$$

Then we have for any $t > 0$,

$$\begin{aligned}
& \mathbb{P}[W_{in} \geq t | \mathcal{F}_n] \\
&\leq \exp(|A(\hat{\theta}_{n,x}(Z_{in}) + a_{in})| + |A(\hat{\theta}_{n,x}(Z_{in}))| + |a_{in}| |A'(\hat{\theta}_{n,x}(Z_{in}))|) \exp(-t) \\
&\leq \exp(\sup_i |A(\hat{\theta}_{n,x}(Z_{in}) + a_{in})| + \sup_i |A(\hat{\theta}_{n,x}(Z_{in}))| + \sup_i |a_{in}| |A'(\hat{\theta}_{n,x}(Z_{in}))|) \exp(-t).
\end{aligned}$$

Choosing

$$\theta_n = \exp \left(\sup_i |A(\hat{\theta}_{n,x}(Z_{in}) + a_{in})| + \sup_i |A(\hat{\theta}_{n,x}(Z_{in}))| + \sup_i |a_{in}| |A'(\hat{\theta}_{n,x}(Z_{in}))| \right)$$

and $\beta = 1$, we need to verify

$$\theta_n = O_{\mathbb{P}}(1) \text{ and } \theta_n < \infty, \text{ almost surely.}$$

Since by condition (11), we know $\sup_i |a_{in}| \leq \sup_i |Y_{in}| + \sup_i |\widehat{\mu}_{n,y}(Z_{in})| < \infty$ almost surely and $|\widehat{\theta}_{n,x}(Z_{in})| < \infty$ almost surely, we know $\theta_n < \infty$ almost surely. Now we prove $\theta_n = O_{\mathbb{P}}(1)$. By condition (CSE), we know for any fixed $\delta > 0$, there exists $M(\delta) > 0$ such that

$$\mathbb{P}[\mathcal{S}] \geq 1 - \delta, \text{ where } \mathcal{S} \equiv \left\{ \sup_i |\widehat{\theta}_{n,x}(Z_{in})|, \sup_i |a_{in}| \in [0, M(\delta)] \right\}.$$

Then on the event \mathcal{S} , we know

$$\sup_i |A(\widehat{\theta}_{n,x}(Z_{in}) + a_{in})| \leq \sup_{x \in [-2M(\delta), 2M(\delta)]} |A(x)|$$

and

$$\sup_i |A'(\widehat{\theta}_{n,x}(Z_{in}))| \leq \sup_{x \in [-M(\delta), M(\delta)]} |A'(x)|.$$

Similarly, on the event \mathcal{S} , we have

$$\sup_i |a_{in}| \leq M(\delta), \quad \sup_i |A(\widehat{\theta}_{n,x}(Z_{in}))| \leq \sup_{x \in [-2M(\delta), 2M(\delta)]} |A(x)|.$$

Therefore we have

$$\mathbb{P}\left[\theta_n \leq \exp\left(2 \sup_{x \in [-2M(\delta), 2M(\delta)]} |A(x)| + M(\delta) \sup_{x \in [-M(\delta), M(\delta)]} |A'(x)|\right)\right] \geq \mathbb{P}[\mathcal{S}] \geq 1 - \delta.$$

Therefore we have $\theta_n = O_{\mathbb{P}}(1)$. Thus $\varepsilon = \beta/8 = 1/8$ according to Lemma 5.

Verification of Assumption 3 with condition (11) and (CCS): By condition (CCS), we know

$$\mathbb{1}(\tilde{X}_{in} \in [-S, S]) = 1, \text{ almost surely.}$$

This implies that for any $F \in \mathcal{F}_n$, we have

$$\int_F \mathbb{1}(\tilde{X}_{in} \in [-S, S]) d\mathbb{P} = \int_F 1 d\mathbb{P}.$$

Thus we know

$$\mathbb{P}[\tilde{X}_{in} \in [-S, S] | \mathcal{F}_n] = \mathbb{E}[\mathbb{1}(\tilde{X}_{in} \in [-S, S]) | \mathcal{F}_n] = 1, \text{ almost surely.}$$

Thus we have

$$\mathbb{P}\left[a_{in}(\tilde{X}_{in} - \widehat{\mu}_{n,x}(Z_{in})) \in [-2|a_{in}|S, 2|a_{in}|S] | \mathcal{F}_n\right] = 1, \text{ almost surely.}$$

Then again by condition (11), we know

$$|a_{in}| \leq |Y_{in}| + |\widehat{\mu}_{n,x}(Z_{in})| < \infty, \text{ almost surely.}$$

Moreover, by condition (CCS), we know

$$\frac{1}{n} \sum_{i=1}^n 16S^4 a_{in}^4 = \frac{16S^4}{n} \sum_{i=1}^n (Y_{in} - \widehat{\mu}_{n,y}(Z_{in}))^4 = O_{\mathbb{P}}(1).$$

Choosing $\nu_{in} = 2|a_{in}|S$, we complete the proof for CCS distribution. Thus $\varepsilon = 1/8$ according to Lemma 5.

D.2 Proof of Theorem 2

Proof of Theorem 2. Define the auxiliary test

$$\phi_{n,\alpha}^{\text{aux}} \equiv \mathbb{1} \left(\frac{n^{1/2} T_n^{\text{dCRT}}(X, Y, Z)}{\widehat{S}_n^{\text{dCRT}}} > \mathbb{Q}_{1-\alpha(1+M_n)} \left[n^{1/2} T_n^{\text{ndCRT}}(\tilde{X}, X, Y, Z) | X, Y, Z \right] \right)$$

where $T_n^{\text{ndCRT}}(\tilde{X}, X, Y, Z)$ is defined in (34) and M_n is the sequence such that

$$\mathbb{P} \left(T_n^{\text{dCRT}}(\tilde{X}, X, Y, Z) \geq T_n^{\text{dCRT}}(X, Y, Z) | \mathcal{F}_n \right) = p_{\text{spaCRT}}(1 + M_n), \text{ almost surely.}$$

Notice the tests $\phi_{n,\alpha}^{\text{spaCRT}}$ and $\phi_{n,\alpha}^{\text{aux}}$ are equivalent as long as $M_n \in (-1, 1/\alpha - 1)$. Indeed, we have

$$\mathbb{P}[\phi_{n,\alpha}^{\text{spaCRT}} \neq \phi_{n,\alpha}^{\text{aux}}] \leq \mathbb{P}[\widehat{S}_n^{\text{dCRT}} = 0] + \mathbb{P}[M_n \notin (-1, 1/\alpha - 1)] \rightarrow 0$$

due to assumption (31) and that $M_n = o_{\mathbb{P}}(1)$. Thus we only need to verify $\phi_{n,\alpha}^{\text{aux}}$ and $\phi_{n,\alpha}^{\text{dCRT}}$ are asymptotically equivalent. To this end, we consider another test

$$\phi_{n,\alpha}^{\text{asy}} \equiv \mathbb{1} \left(\frac{n^{1/2} T_n^{\text{dCRT}}(X, Y, Z)}{\widehat{S}_n^{\text{dCRT}}} > z_{1-\alpha} \right).$$

We will prove $\phi_{n,\alpha}^{\text{aux}}, \phi_{n,\alpha}^{\text{asy}}$ are asymptotically equivalent and $\phi_{n,\alpha}^{\text{dCRT}}, \phi_{n,\alpha}^{\text{asy}}$ are asymptotically equivalent, respectively.

Proof of the equivalence of $\phi_{n,\alpha}^{\text{aux}}, \phi_{n,\alpha}^{\text{asy}}$: We apply Lemma 7 with the test statistic $T_n(X, Y, Z)$ to be

$$T_n(X, Y, Z) \equiv \frac{n^{1/2} T_n^{\text{dCRT}}(X, Y, Z)}{\widehat{S}_n^{\text{dCRT}}}$$

and cutoff $C_n(X, Y, Z)$ to be

$$C_n(X, Y, Z) \equiv \mathbb{Q}_{1-\alpha(1+M_n)} \left[n^{1/2} T_n^{\text{ndCRT}}(\tilde{X}, X, Y, Z) | X, Y, Z \right].$$

The following lemma characterizes the convergence of $C_n(X, Y, Z)$.

Lemma 13. Suppose the sequence of laws \mathcal{L}_n and its estimate $\widehat{\mathcal{L}}_n$ satisfy all the assumptions in **Regularity condition**. Then for any given $\alpha \in (0, 1)$, we have for any sequence $M_n \in \mathcal{F}_n$ satisfying $M_n = o_{\mathbb{P}}(1)$,

$$\mathbb{Q}_{1-\alpha(1+M_n)} \left[n^{1/2} T_n^{\text{ndCRT}}(\tilde{X}, X, Y, Z) | X, Y, Z \right] \xrightarrow{\mathbb{P}} z_{1-\alpha}$$

where $T_n^{\text{ndCRT}}(\tilde{X}, X, Y, Z)$ is defined as in (34).

To apply Lemma 13 (as well as Lemma 8), we will first verify condition (31)-(33) in **Regularity condition** are satisfied under the assumptions of Theorem 2.

Verification of (31): This is true by assumption (12).

Verification of (32): We verify the condition when $\delta = 2$. When condition (CSE) holds, it suffices to prove

$$\frac{1}{n^2} \sum_{i=1}^n \mathbb{E}_{\hat{\mathcal{L}}_n} [|\tilde{X}_{in} - \hat{\mu}_{n,x}(Z_{in})|^4 | X, Z] = o_{\mathbb{P}}(1).$$

By Lemma 4, we know

$$\mathbb{E}_{\hat{\mathcal{L}}_n} [|\tilde{X}_{in} - \hat{\mu}_{n,x}(Z_{in})|^4 | X, Z] = A^{(4)}(\hat{\theta}_{n,x}(Z_{in})) + 3(A''(\hat{\theta}_{n,x}(Z_{in})))^2.$$

Since by condition (CSE), $\sup_i |\hat{\theta}_{n,x}(Z_{in})| = O_{\mathbb{P}}(1)$, we know there exists $\delta > 0$ such that

$$\mathbb{P}[\mathcal{L}] \geq 1 - \delta, \text{ where } \mathcal{L} \equiv \left\{ \sup_i |\hat{\theta}_{n,x}(Z_{in})| \leq M(\delta) \right\}.$$

Then on the event \mathcal{L} , by the smoothness of function A , we have

$$\begin{aligned} \sup_i |A^{(4)}(\hat{\theta}_{n,x}(Z_{in}))| &\leq \sup_{x \in [-M(\delta), M(\delta)]} |A^{(4)}(x)| < \infty, \\ \sup_i |A^{(2)}(\hat{\theta}_{n,x}(Z_{in}))| &\leq \sup_{x \in [-M(\delta), M(\delta)]} |A^{(2)}(x)| < \infty. \end{aligned}$$

Thus we know for any $\delta > 0$,

$$\begin{aligned} \mathbb{P} \left[\sup_i |A^{(4)}(\hat{\theta}_{n,x}(Z_{in}))| \leq \sup_{x \in [-M(\delta), M(\delta)]} |A^{(4)}(x)| < \infty \right] &\geq \mathbb{P}[\mathcal{L}] \geq 1 - \delta \\ \mathbb{P} \left[\sup_i |A^{(2)}(\hat{\theta}_{n,x}(Z_{in}))| \leq \sup_{x \in [-M(\delta), M(\delta)]} |A^{(2)}(x)| < \infty \right] &\geq \mathbb{P}[\mathcal{L}] \geq 1 - \delta \end{aligned}$$

This implies

$$\sup_i |A^{(4)}(\hat{\theta}_{n,x}(Z_{in}))| = O_{\mathbb{P}}(1), \quad \sup_i |A^{(2)}(\hat{\theta}_{n,x}(Z_{in}))| = O_{\mathbb{P}}(1).$$

Thus we have

$$\begin{aligned} \frac{1}{n^2} \sum_{i=1}^n \mathbb{E}_{\hat{\mathcal{L}}_n} [|\tilde{X}_{in} - \hat{\mu}_{n,x}(Z_{in})|^4 | X, Z] &\leq \frac{1}{n} \left(\sup_i |A^{(4)}(\hat{\theta}_{n,x}(Z_{in}))| + 3 \sup_i (A''(\hat{\theta}_{n,x}(Z_{in})))^2 \right) \\ &= o_{\mathbb{P}}(1). \end{aligned}$$

When condition (CCS) holds, it suffices to prove

$$\frac{1}{n^2} \sum_{i=1}^n (Y_{in} - \hat{\mu}_{n,y}(Z_{in}))^4 = o_{\mathbb{P}}(1).$$

This is true by the condition (CCS).

Verification of (33): $\text{Var}_{\hat{\mathcal{L}}_n}[X_{in}|Z_{in}] = A''(\hat{\theta}(Z_{in})) < \infty$ and $(Y_{in} - \hat{\mu}_{n,y}(Z_{in}))^2 < \infty$ almost surely can be guaranteed respectively by $|\hat{\theta}(Z_{in})| < \infty$ and $|a_{in}| < \infty$ almost surely in assumption (43). As for $(Y_{in} - \mu_{n,y}(Z_{in}))^2 < \infty$, it is true by the integrability of Y_{in} .

Therefore, applying Lemma 13, we have

$$\mathbb{Q}_{1-\alpha(1+M_n)} \left[n^{1/2} T_n^{\text{ndCRT}}(\tilde{X}, X, Y, Z) | X, Y, Z \right] \xrightarrow{\mathbb{P}} z_{1-\alpha}.$$

Moreover, the condition (30) holds for the chosen $T_n(X, Y, Z)$ by condition (16) so that this proves the asymptotic equivalence of $\phi_{n,\alpha}^{\text{aux}}$ and $\phi_{n,\alpha}^{\text{asy}}$.

Proof of the equivalence of $\phi_{n,\alpha}^{\text{aux}}, \phi_{n,\alpha}^{\text{dCRT}}$: In order to prove the asymptotic equivalence between $\phi_{n,\alpha}^{\text{dCRT}}$ and $\phi_{n,\alpha}^{\text{asy}}$, we apply Lemma 7 with the test statistic $T_n(X, Y, Z)$ to be

$$T_n(X, Y, Z) \equiv \frac{n^{1/2} T_n^{\text{dCRT}}(X, Y, Z)}{\hat{S}_n^{\text{dCRT}}}$$

and cutoff $C_n(X, Y, Z)$ to be

$$C_n(X, Y, Z) \equiv \mathbb{Q}_{1-\alpha} \left[n^{1/2} T_n^{\text{ndCRT}}(\tilde{X}, X, Y, Z) | X, Y, Z \right].$$

By Lemma 8, we have proved that under the assumptions in Theorem 2,

$$\mathbb{Q}_{1-\alpha} \left[n^{1/2} T_n^{\text{ndCRT}}(\tilde{X}, X, Y, Z) | X, Y, Z \right] \xrightarrow{\mathbb{P}} z_{1-\alpha}.$$

Similarly, the nonaccumulant assumption (30) has been satisfied by (16) so that we have proved the asymptotic equivalence between $\phi_{n,\alpha}^{\text{dCRT}}$ and $\phi_{n,\alpha}^{\text{asy}}$. \square

D.3 Proof of Corollary 1

Proof of Corollary 1. For any $\varepsilon > 0$,

$$\begin{aligned} \mathbb{P}_{H_0}[p_{\text{spaCRT}} \leq \alpha] &= \mathbb{P}_{H_0}[p_{\text{spaCRT}} \leq 0] + \mathbb{P}_{H_0}[p_{\text{spaCRT}} \in (0, \alpha)] \\ &= \mathbb{P}_{H_0}[p_{\text{spaCRT}} \leq 0] + \mathbb{P}_{H_0}[p_{\text{spaCRT}} \in (0, \alpha), p_{\text{dCRT}}/p_{\text{spaCRT}} \leq 1 + \varepsilon] \\ &\quad + \mathbb{P}_{H_0}[p_{\text{spaCRT}} \in (0, \alpha), p_{\text{dCRT}}/p_{\text{spaCRT}} > 1 + \varepsilon] \\ &\leq \mathbb{P}_{H_0}[p_{\text{spaCRT}} \leq 0] + \mathbb{P}_{H_0}[p_{\text{dCRT}}/p_{\text{spaCRT}} > 1 + \varepsilon] \\ &\quad + \mathbb{P}_{H_0}[p_{\text{dCRT}} \leq \alpha(1 + \varepsilon)]. \end{aligned}$$

By the asymptotic validity of dCRT, $\lim_{n \rightarrow \infty} \mathbb{P}_{H_0}[p_{\text{dCRT}} \leq \alpha] \leq \alpha$, and conclusion (14) in Theorem 1, we have

$$\lim_{n \rightarrow \infty} \mathbb{P}_{H_0}[p_{\text{spaCRT}} \leq \alpha] \leq \alpha(1 + \varepsilon) + 0 + \lim_{n \rightarrow \infty} \mathbb{P}_{H_0}[p_{\text{spaCRT}} \leq 0].$$

By conclusion (15), we prove

$$\lim_{n \rightarrow \infty} \mathbb{P}_{H_0}[p_{\text{spaCRT}} \leq \alpha] \leq \alpha(1 + \varepsilon).$$

Since $\varepsilon > 0$ is arbitrary, we have $\lim_{n \rightarrow \infty} \mathbb{P}_{H_0}[p_{\text{spaCRT}} \leq \alpha] \leq \alpha$. Therefore, spaCRT is asymptotic valid. \square

D.4 Proof of Lemma 1

Proof of Lemma 1. We verify the conditions in Theorem 1.

Verification of (11): We first show $|\theta(Z_{in})| < \infty$ almost surely. This is true because $\mathbb{E}[X_{in}|Z_{in}] = \text{expit}(\theta(Z_{in}))$ and $|\mathbb{E}[X_{in}|Z_{in}]| < \infty$ almost surely. Then together with $|\widehat{\theta}_{n,x}(Z_{in}) - \theta(Z_{in})| \xrightarrow{a.s.} 0$ in assumption (18), we have

$$|\widehat{\theta}_{n,x}(Z_{in})| \leq |\widehat{\theta}_{n,x}(Z_{in}) - \theta(Z_{in})| + |\theta(Z_{in})| < \infty, \text{ almost surely.}$$

We now show $\sup_n \mathbb{E}[(Y_{in} - \mu_{n,y}(Z_{in}))^2] < \infty$. This implies

$$|Y_{in} - \mu_{n,y}(Z_{in})| < \infty, \forall i \in [n], n \in \mathbb{N}_+ \text{ almost surely.} \quad (37)$$

This is true by using Jensen's inequality (Lemma 12) and Cauchy-Schwarz inequality:

$$\begin{aligned} \sup_n \mathbb{E}[(Y_{in} - \mu_{n,y}(Z_{in}))^2] &\leq 2 \sup_n (\mathbb{E}[Y_{in}^2] + \mathbb{E}[\mu_{n,y}(Z_{in})^2]) \\ &\leq 2 \sup_n (\mathbb{E}[Y_{in}^2] + \mathbb{E}[Y_{in}^2]) = 4 \sup_n \mathbb{E}[Y_{in}^2] \leq 4 \sqrt{\sup_n \mathbb{E}[Y_{in}^4]} < \infty. \end{aligned}$$

Then by $|\widehat{\mu}_{n,y}(Z_{in}) - \mu_{n,y}(Z_{in})| \xrightarrow{a.s.} 0$ in assumption (18), we have

$$|a_{in}| = |Y_{in} - \widehat{\mu}_{n,y}(Z_{in})| \leq |Y_{in} - \mu_{n,y}(Z_{in})| + |\widehat{\mu}_{n,y}(Z_{in}) - \mu_{n,y}(Z_{in})| < \infty$$

almost surely.

Verification of (12): We can write

$$\begin{aligned} \frac{1}{n} \sum_{i=1}^n a_{in}^2 A''(\widehat{\theta}_{n,x}(Z_{in})) &= \frac{1}{n} \sum_{i=1}^n a_{in}^2 A''(\theta(Z_{in})) + \frac{1}{n} \sum_{i=1}^n a_{in} (A''(\widehat{\theta}_{n,x}(Z_{in})) - A''(\theta(Z_{in}))) \\ &\equiv T_1 + T_2. \end{aligned}$$

We will first prove $T_2 = o_{\mathbb{P}}(1)$. To see this, we notice that $A''(x) = \exp(x)/(1+\exp(x))^2$ and it can be easily checked that $A''(x)$ is a lipschitz function with Lipschitz constant 1. Thus we have

$$|T_2| \leq \frac{1}{n} \sum_{i=1}^n a_{in}^2 |\widehat{\theta}_{n,x}(Z_{in}) - \theta(Z_{in})| \leq \sqrt{\frac{1}{n} \sum_{i=1}^n a_{in}^4} \sqrt{\frac{1}{n} \sum_{i=1}^n |\widehat{\theta}_{n,x}(Z_{in}) - \theta(Z_{in})|^2}.$$

Thus it suffces to show

$$\frac{1}{n} \sum_{i=1}^n a_{in}^4 = O_{\mathbb{P}}(1), \quad \frac{1}{n} \sum_{i=1}^n |\widehat{\theta}_{n,x}(Z_{in}) - \theta(Z_{in})|^2 = o_{\mathbb{P}}(1). \quad (38)$$

By assumption (17), it suffcies to show $\frac{1}{n} \sum_{i=1}^n a_{in}^4 = O_{\mathbb{P}}(1)$. In fact, we have

$$\frac{1}{n} \sum_{i=1}^n a_{in}^4 \leq \frac{16}{n} \sum_{i=1}^n (Y_{in} - \mu_{n,y}(Z_{in}))^4 + \frac{16}{n} \sum_{i=1}^n (\widehat{\mu}_{n,y}(Z_{in}) - \mu_{n,y}(Z_{in}))^4.$$

By the convergence of $\widehat{\mu}_{n,y}(Z_{in})$ in assumption (17), it suffices to show $\sup_n \mathbb{E}[(Y_{in} - \mu_{n,y}(Z_{in}))^4] < \infty$. This is guaranteed by assumption (19) and Jensen's inequality (Lemma 12):

$$\begin{aligned}\sup_n \mathbb{E}[(Y_{in} - \mu_{n,y}(Z_{in}))^4] &\leq 16 \sup_n (\mathbb{E}[Y_{in}^4] + \mathbb{E}[\mathbb{E}[Y_{in} | Z_{in}]^4]) \\ &\leq 16 \sup_n (\mathbb{E}[Y_{in}^4] + \mathbb{E}[Y_{in}^4]) = 32 \sup_n \mathbb{E}[Y_{in}^4] < \infty.\end{aligned}$$

Therefore, we have proved $T_2 = o_{\mathbb{P}}(1)$ and now we prove $T_1 = \Omega_{\mathbb{P}}(1)$. We first decompose

$$T_1 = \frac{1}{n} \sum_{i=1}^n (Y_{in} - \widehat{\mu}_{n,y}(Z_{in}))^2 A''(\theta(Z_{in})) \equiv \frac{1}{n} \sum_{i=1}^n (Y_{in} - \mu_{n,y}(Z_{in}))^2 A''(\theta(Z_{in})) + T_3$$

where

$$T_3 \equiv \frac{1}{n} \sum_{i=1}^n \{(Y_{in} - \widehat{\mu}_{n,y}(Z_{in}))^2 - (Y_{in} - \mu_{n,y}(Z_{in}))^2\} A''(\theta(Z_{in})).$$

Then by the boundedness of A'' , we have

$$\begin{aligned}|T_3| &\leq \frac{1}{n} \sum_{i=1}^n |\widehat{\mu}_{n,y}(Z_{in}) - \mu_{n,y}(Z_{in})| |2Y_{in} - \mu_{n,y}(Z_{in}) - \widehat{\mu}_{n,y}(Z_{in})| \\ &\leq \sqrt{\frac{1}{n} \sum_{i=1}^n (\widehat{\mu}_{n,y}(Z_{in}) - \mu_{n,y}(Z_{in}))^2} \sqrt{\frac{2}{n} \sum_{i=1}^n (Y_{in} - \mu_{n,y}(Z_{in}))^2 + \frac{2}{n} \sum_{i=1}^n a_{in}^2}.\end{aligned}$$

We have shown in above that

$$\frac{1}{n} \sum_{i=1}^n (Y_{in} - \mu_{n,y}(Z_{in}))^2 = O_{\mathbb{P}}(1), \quad \frac{1}{n} \sum_{i=1}^n a_{in}^2 = O_{\mathbb{P}}(1).$$

Then by assumption (17), we have

$$\frac{1}{n} \sum_{i=1}^n (\widehat{\mu}_{n,y}(Z_{in}) - \mu_{n,y}(Z_{in}))^2 \leq \sqrt{\frac{1}{n} \sum_{i=1}^n (\widehat{\mu}_{n,y}(Z_{in}) - \mu_{n,y}(Z_{in}))^4} = o_{\mathbb{P}}(1).$$

Thus we have proved $T_3 = o_{\mathbb{P}}(1)$. The final step is to prove

$$\frac{1}{n} \sum_{i=1}^n (Y_{in} - \mu_{n,y}(Z_{in}))^2 A''(\theta(Z_{in})) = \Omega_{\mathbb{P}}(1).$$

We apply weak law of large numbers to triangular arrays to conclude the proof. In particular, we apply Lemma 9 with $\delta = 1$ so we need to verify

$$\sup_n \mathbb{E}[(Y_{in} - \mu_{n,y}(Z_{in}))^4 (A''(\theta(Z_{in})))^4] < \infty.$$

Since $|A''(x)| \leq 1$ for any $x \in \mathbb{R}$, by assumption (19), we have

$$\begin{aligned} \sup_n \mathbb{E}[(Y_{in} - \mu_{n,y}(Z_{in}))^4 (A''(\theta(Z_{in})))^2] &\leq \sup_n \mathbb{E}[(Y_{in} - \mu_{n,y}(Z_{in}))^4] \\ &\leq 32 \sup_n \mathbb{E}[Y_{in}^4] < \infty. \end{aligned}$$

Therefore, applying Lemma 9 and assumption 1 we obtain

$$\frac{1}{n} \sum_{i=1}^n (Y_{in} - \mu_{n,y}(Z_{in}))^2 A''(\theta(Z_{in})) = o_{\mathbb{P}}(1) + \mathbb{E}[(Y_{in} - \mu_{n,y}(Z_{in}))^2 A''(\theta(Z_{in}))] = \Omega_{\mathbb{P}}(1).$$

Verification of condition (CCS): Since $\mathbb{P}[\tilde{X}_{in} \in [-1, 1] | \mathcal{F}_n] = 1$ almost surely, it suffices to show

$$\frac{1}{n} \sum_{i=1}^n a_{in}^4 = \frac{1}{n} \sum_{i=1}^n (Y_{in} - \hat{\mu}_{n,y}(Z_{in}))^4 = O_{\mathbb{P}}(1).$$

This has been proved in conclusion (38). \square

D.5 Proof of Lemma 2

Before proving Lemma 2, we first present two lemmas that will be used in the proof of Lemma 2.

Lemma 14. Under the assumptions (20)-(23) in Lemma 2, for any $p, s \in \mathbb{N}$ and $p \geq 1, s \geq 0$, we have

$$\sup_n \mathbb{E}[|g^{(s)}(Z_{in}^\top \beta_n)|^p] < \infty, \quad \sup_{i,n} |g^{(s)}(Z_{in}^\top \beta_n)|^p = O_{\mathbb{P}}(1) \quad (39)$$

$$\sup_n \mathbb{E}[|h^{(s)}(Z_{in}^\top \beta_n)|^p] < \infty, \quad \sup_{i,n} |h^{(s)}(Z_{in}^\top \alpha_n)|^p = O_{\mathbb{P}}(1) \quad (40)$$

and

$$\sup_i |g^{(s)}(Z_{in}^\top \hat{\beta}_n) - g^{(s)}(Z_{in}^\top \beta_n)| \xrightarrow{\text{a.s.}} 0, \quad \sup_i |h^{(s)}(Z_{in}^\top \hat{\alpha}_n) - h^{(s)}(Z_{in}^\top \alpha_n)| \xrightarrow{\text{a.s.}} 0. \quad (41)$$

Furthermore, we have

$$\sup_i |g^{(s)}(Z_{in}^\top \hat{\beta}_n)|^p = O_{\mathbb{P}}(1), \quad \sup_i |h^{(s)}(Z_{in}^\top \hat{\alpha}_n)|^p = O_{\mathbb{P}}(1). \quad (42)$$

Lemma 15. Under the assumptions (20)-(23) in Lemma 2, we have $\sup_n \mathbb{E}[|Y_{in}|^p] < \infty$ and $\sup_n \mathbb{E}[|X_{in}|^p] < \infty$ for any $p \in \mathbb{N}$.

Now we are ready to prove Lemma 2.

Proof of Lemma 2. We need to verify the conditions in Theorem 1.

Verification of (11): We will only need to prove $|\widehat{\theta}_{n,x}(Z_{in})| = |Z_{in}^\top \widehat{\alpha}_n| < \infty$ and $|a_{in}| = |Y_{in} - g(Z_{in}^\top \widehat{\beta}_n)| < \infty$ almost surely. For the first claim, it is obvious since $|Z_{in}^\top \widehat{\alpha}_n| \leq \|Z_{in}\|_\infty \|\widehat{\alpha}_n\|_1$ and $\|\widehat{\alpha}_n\|_1 \leq \|\widehat{\alpha}_n - \alpha_n\|_1 + \|\alpha_n\|_1 < \infty$ by assumptions (23) and (22). Together with the assumption (20), we know $\|Z_{in}\|_\infty \leq C_Z$ so that $|\widehat{\theta}_{n,x}(Z_{in})| < \infty$ almost surely. For the second claim, we have bound

$$|Y_{in} - g(Z_{in}^\top \widehat{\beta}_n)| \leq |Y_{in} - g(Z_{in}^\top \beta_n)| + |g(Z_{in}^\top \beta_n) - g(Z_{in}^\top \widehat{\beta}_n)|.$$

To bound the term $|g(Z_{in}^\top \beta_n) - g(Z_{in}^\top \widehat{\beta}_n)|$, we use (41) in Lemma 14 so that we know $|g(Z_{in}^\top \beta_n) - g(Z_{in}^\top \widehat{\beta}_n)|$ converges to 0 almost surely. For the term $|Y_{in} - g(Z_{in}^\top \beta_n)|$, we know $\mathbb{E}[|Y_{in} - g(Z_{in}^\top \beta_n)|^2] = \mathbb{E}[g'(Z_{in}^\top \beta_n)] \leq \sup_n \mathbb{E}[|g'(Z_{in}^\top \beta_n)|] < \infty$ by (39) in Lemma 14. Thus we have proved

$$|a_{in}| = |Y_{in} - g(Z_{in}^\top \widehat{\beta}_n)| < \infty \text{ and } |Y_{in} - g(Z_{in}^\top \beta_n)| < \infty \text{ almost surely.} \quad (43)$$

This completes the proof.

Verification of (12): We write

$$\begin{aligned} \frac{1}{n} \sum_{i=1}^n a_{in}^2 A''(\widehat{\theta}_{n,x}(Z_{in})) &= \frac{1}{n} \sum_{i=1}^n (Y_{in} - g(Z_{in}^\top \widehat{\beta}_n))^2 h'(Z_{in}^\top \widehat{\alpha}_n) \\ &\equiv \frac{1}{n} \sum_{i=1}^n (Y_{in} - g(Z_{in}^\top \beta_n))^2 h'(Z_{in}^\top \alpha_n) + I_n. \end{aligned}$$

where

$$\begin{aligned} I_n &= \frac{1}{n} \sum_{i=1}^n \left\{ (Y_{in} - g(Z_{in}^\top \widehat{\beta}_n))^2 - (Y_{in} - g(Z_{in}^\top \beta_n))^2 \right\} h'(Z_{in}^\top \alpha_n) \\ &\quad + \frac{1}{n} \sum_{i=1}^n (Y_{in} - g(Z_{in}^\top \widehat{\beta}_n))^2 (h'(Z_{in}^\top \widehat{\alpha}_n) - h'(Z_{in}^\top \alpha_n)) \\ &\equiv I_{n,1} + I_{n,2}. \end{aligned}$$

For $I_{n,1}$, we can bound

$$\begin{aligned} |I_{n,1}| &\leq \frac{1}{n} \sum_{i=1}^n |g^2(Z_{in}^\top \widehat{\beta}_n) - g^2(Z_{in}^\top \beta_n) + 2Y_{in}(g(Z_{in}^\top \beta_n) - g(Z_{in}^\top \widehat{\beta}_n))| h'(Z_{in}^\top \alpha_n) \\ &\leq \frac{O_{\mathbb{P}}(1)}{n} \sum_{i=1}^n |g^2(Z_{in}^\top \widehat{\beta}_n) - g^2(Z_{in}^\top \beta_n) + 2Y_{in}(g(Z_{in}^\top \beta_n) - g(Z_{in}^\top \widehat{\beta}_n))| \\ &\leq O_{\mathbb{P}}(1) \left(\sup_i |g^2(Z_{in}^\top \widehat{\beta}_n) - g^2(Z_{in}^\top \beta_n)| + \sup_i |g(Z_{in}^\top \widehat{\beta}_n) - g(Z_{in}^\top \beta_n)| \frac{2}{n} \sum_{i=1}^n |Y_{in}| \right) \end{aligned}$$

where the second inequality is due to (40) in Lemma 14. Now we consider

$$\begin{aligned} \sup_i |g^2(Z_{in}^\top \widehat{\beta}_n) - g^2(Z_{in}^\top \beta_n)| &= \sup_i |g(Z_{in}^\top \widehat{\beta}_n) - g(Z_{in}^\top \beta_n)| |g(Z_{in}^\top \widehat{\beta}_n) + g(Z_{in}^\top \beta_n)| \\ &= \sup_i |g(Z_{in}^\top \widehat{\beta}_n) - g(Z_{in}^\top \beta_n)| O_{\mathbb{P}}(1) \\ &= o_{\mathbb{P}}(1) \cdot O_{\mathbb{P}}(1) = o_{\mathbb{P}}(1). \end{aligned}$$

where the second equality is due to (39) and (42) in Lemma 14 and the second last equality is due to (41) in Lemma 14. Then to prove $I_{n,1} = o_{\mathbb{P}}(1)$, it suffices to prove

$$\frac{1}{n} \sum_{i=1}^n |Y_{in}| \leq \sqrt{\frac{1}{n} \sum_{i=1}^n Y_{in}^2} = O_{\mathbb{P}}(1). \quad (44)$$

This is true by applying Lemma 15 with $p = 2$. Now we prove $I_{n,2} = o_{\mathbb{P}}(1)$. We first bound

$$\begin{aligned} |I_{n,2}| &\leq \sup_i |h'(Z_{in}^\top \hat{\alpha}_n) - h'(Z_{in}^\top \alpha_n)| \left(\frac{1}{n} \sum_{i=1}^n (Y_{in} - g(Z_{in}^\top \hat{\beta}_n))^2 \right) \\ &\leq o_{\mathbb{P}}(1) \left(\frac{2}{n} \sum_{i=1}^n Y_{in}^2 + \frac{2}{n} \sum_{i=1}^n g^2(Z_{in}^\top \hat{\beta}_n) \right) \\ &= o_{\mathbb{P}}(1) \cdot O_{\mathbb{P}}(1) = o_{\mathbb{P}}(1). \end{aligned}$$

where the second inequality is due to (41) in Lemma 14 and the second last inequality is due to (44) and (42) in Lemma 14. Therefore, we have proved

$$\frac{1}{n} \sum_{i=1}^n a_{in}^2 A''(\hat{\theta}_{n,x}(Z_{in})) = \frac{1}{n} \sum_{i=1}^n (Y_{in} - g(Z_{in}^\top \beta_n))^2 h'(Z_{in}^\top \alpha_n) + o_{\mathbb{P}}(1).$$

Now we apply Lemma 9 to conclude the proof with $\delta = 1$. Thus it suffices to verify

$$\sup_n \mathbb{E}[(Y_{in} - g(Z_{in}^\top \beta_n))^4 (h'(Z_{in}^\top \alpha_n))^2] < \infty. \quad (45)$$

Equivalently, by Lemma 4 and Cauchy-Schwarz inequality, we need to verify

$$\begin{aligned} &\sup_n \mathbb{E}[(Y_{in} - g(Z_{in}^\top \beta_n))^4 (h'(Z_{in}^\top \alpha_n))^2] \\ &= \sup_n \mathbb{E}[\mathbb{E}[(Y_{in} - g(Z_{in}^\top \beta_n))^4 | Z_{in}] (h'(Z_{in}^\top \alpha_n))^2] \\ &= \sup_n \mathbb{E}[(g^{(3)}(Z_{in}^\top \beta_n) + 3(g'(Z_{in}^\top \beta_n))^2)(h'(Z_{in}^\top \alpha_n))^2] \\ &\leq \sqrt{\sup_n \mathbb{E}[(g^{(3)}(Z_{in}^\top \beta_n) + 3(g'(Z_{in}^\top \beta_n))^2)^2]} \sqrt{\sup_n \mathbb{E}[(h'(Z_{in}^\top \alpha_n))^4]} \\ &< \infty. \end{aligned}$$

We first verify $\sup_n \mathbb{E}[(g^{(3)}(Z_{in}^\top \beta_n) + 3(g'(Z_{in}^\top \beta_n))^2)^2] < \infty$. By (39) in Lemma 14, we have

$$\begin{aligned} \sup_n \mathbb{E}[(g^{(3)}(Z_{in}^\top \beta_n) + 3(g'(Z_{in}^\top \beta_n))^2)^2] &\leq 2 \sup_n (\mathbb{E}[(g^{(3)}(Z_{in}^\top \beta_n))^2] + 9\mathbb{E}[(g'(Z_{in}^\top \beta_n))^4]) \\ &< \infty. \end{aligned}$$

Now we verify $\sup_n \mathbb{E}[(h'(Z_{in}^\top \alpha_n))^4] < \infty$. By (40) in Lemma 14, $\sup_n \mathbb{E}[(h'(Z_{in}^\top \alpha_n))^4] < \infty$. Thus we have verified (45) so that by Lemma 9

$$\frac{1}{n} \sum_{i=1}^n (Y_{in} - g(Z_{in}^\top \beta_n))^2 h'(Z_{in}^\top \alpha_n) - \mathbb{E}[(Y_{in} - g(Z_{in}^\top \beta_n))^2 h'(Z_{in}^\top \alpha_n)] = o_{\mathbb{P}}(1).$$

By Assumption 1, we know

$$\begin{aligned} \frac{1}{n} \sum_{i=1}^n a_{in}^2 A''(\hat{\theta}_{n,x}(Z_{in})) &= \mathbb{E}[(Y_{in} - g(Z_{in}^\top \beta_n))^2 h'(Z_{in}^\top \alpha_n)] + o_{\mathbb{P}}(1) \\ &= \mathbb{E}[(\mathbf{X} - \mathbb{E}[\mathbf{X} | \mathbf{Z}])^2 (\mathbf{Y} - \mathbb{E}[\mathbf{Y} | \mathbf{Z}])^2] + o_{\mathbb{P}}(1) = \Omega_{\mathbb{P}}(1). \end{aligned}$$

Verification of condition (CSE): By condition (21), it suffices to verify

$$\sup_i |\hat{\theta}_{n,x}(Z_{in})| = \sup_i |Z_{in}^\top \hat{\alpha}_n| = O_{\mathbb{P}}(1), \quad \sup_i |\hat{\mu}_{n,y}(Z_{in})| = \sup_i |g(Z_{in}^\top \hat{\beta}_n)| = O_{\mathbb{P}}(1).$$

Since $\|\hat{\alpha}_n - \alpha_n\|_1 = o_{\mathbb{P}}(1)$, $\sup_n \|\alpha_n\|_1 < \infty$, we know together with condition (20),

$$\sup_i |Z_{in}^\top \hat{\alpha}_n| \leq \|Z_{in}\|_\infty \|\hat{\alpha}_n\|_1 \leq \|Z_{in}\|_\infty (\|\hat{\alpha}_n - \alpha_n\|_1 + \|\alpha_n\|_1) = O_{\mathbb{P}}(1).$$

By conclusion (42) with $s = 0, p = 1$, we have $\sup_i |g(Z_{in}^\top \hat{\beta}_n)| = O_{\mathbb{P}}(1)$ so we conclude the proof. \square

D.6 Proof of Lemma 13

Proof of Lemma 13. For any given $\varepsilon \in (0, \min\{1/\alpha - 1, 1\})$, $\eta > 0$, there exists $N(\varepsilon, \eta)$ such that

$$\mathbb{P}[|M_n| > \varepsilon] < \eta, \quad \forall n \geq N(\varepsilon, \eta).$$

We will use T_n^{ndCRT} to denote $T_n^{\text{ndCRT}}(\tilde{X}, X, Y, Z)$. Then consider the $1 - \alpha(1 - \varepsilon)$ and $1 - \alpha(1 + \varepsilon)$ quantiles, we have with probability at least $1 - \eta$, for large enough n , the following is true:

$$\mathbb{Q}_{1-\alpha(1-\varepsilon)}[T_n^{\text{ndCRT}}|X, Y, Z] \geq \mathbb{Q}_{1-\alpha(1+M_n)}[T_n^{\text{ndCRT}}|X, Y, Z] \geq \mathbb{Q}_{1-\alpha(1+\varepsilon)}[T_n^{\text{ndCRT}}|X, Y, Z].$$

Then with probability at least $1 - \eta$, for sufficiently large n , we have

$$|\mathbb{Q}_{1-\alpha(1+M_n)}[T_n^{\text{ndCRT}}|X, Y, Z] - z_{1-\alpha}| \leq A_n + B_n \tag{46}$$

where

$$A_n \equiv |\mathbb{Q}_{1-\alpha(1-\varepsilon)}[T_n^{\text{ndCRT}}|X, Y, Z] - z_{1-\alpha}|, \quad B_n \equiv |\mathbb{Q}_{1-\alpha(1+\varepsilon)}[T_n^{\text{ndCRT}}|X, Y, Z] - z_{1-\alpha}|.$$

Applying Lemma 8, we have

$$\mathbb{Q}_{1-\alpha(1-\varepsilon)}[T_n^{\text{ndCRT}}|X, Y, Z] \xrightarrow{\mathbb{P}} z_{1-\alpha(1-\varepsilon)}, \quad \mathbb{Q}_{1-\alpha(1+\varepsilon)}[T_n^{\text{ndCRT}}|X, Y, Z] \xrightarrow{\mathbb{P}} z_{1-\alpha(1+\varepsilon)}.$$

Thus for the given ε and sufficiently large n , we have with probability at least $1 - \eta$,

$$A_n < \varepsilon + |z_{1-\alpha(1-\varepsilon)} - z_{1-\alpha}|, \quad B_n < \varepsilon + |z_{1-\alpha(1+\varepsilon)} - z_{1-\alpha}|.$$

By the continuity of the quantile function of standard normal distribution, we know there exists a universal constant C_α that only depends on α such that

$$|z_{1-\alpha(1+\varepsilon)} - z_{1-\alpha}| < C_\alpha \varepsilon, \quad |z_{1-\alpha(1-\varepsilon)} - z_{1-\alpha}| < C_\alpha \varepsilon.$$

Then combining (46), we know with probability at least $1 - 2\eta$, for sufficiently large n , we have

$$|\mathbb{Q}_{1-\alpha(1+M_n)}[T_n^{\text{ndCRT}}|X, Y, Z] - z_{1-\alpha}| \leq A_n + B_n < 2C_\alpha \varepsilon + 2\varepsilon.$$

Then since η, ε is arbitrary, we have

$$\mathbb{Q}_{1-\alpha(1+M_n)}[T_n^{\text{ndCRT}}(\tilde{X}, X, Y, Z)|X, Y, Z] = \mathbb{Q}_{1-\alpha(1+M_n)}[T_n^{\text{ndCRT}}|X, Y, Z] \xrightarrow{\mathbb{P}} z_{1-\alpha}.$$

Therefore we complete the proof. \square

D.7 Proof of Lemma 14

Proof of Lemma 14. We prove claims (39)-(42) separately. We will only prove the results for g as the proof for h is similar.

Proof of (39) and (40): By assumption (23), we know

$$|Z_{in}^\top \beta_n| \leq \|Z_{in}\|_\infty \|\beta_n\|_1 \leq C_Z \sup_n \|\beta_n\|_1 < \infty$$

Then defining $\mathcal{A} \equiv [-C_Z \sup_n \|\beta_n\|_1, C_Z \sup_n \|\beta_n\|_1]$, by the continuity of $|g^{(s)}(\cdot)|$ in the compact domain \mathcal{A} , we have

$$\sup_{i,n} |g^{(s)}(Z_{in}^\top \beta_n)|^p \leq \sup_{a \in \mathcal{A}} |g^{(s)}(a)|^p < \infty, \quad \sup_n \mathbb{E}[|g^{(s)}(Z_{in}^\top \beta_n)|^p] \leq \sup_{a \in \mathcal{A}} |g^{(s)}(a)|^p < \infty.$$

Proof of (41): Assumption (22) ensures that for almost every $\omega \in \Omega$, there exists large enough $N(\omega)$ so that $\forall n \geq N(\omega)$,

$$|Z_{in}^\top(\omega) \hat{\beta}_n(\omega) - Z_{in}^\top(\omega) \beta_n| \leq \|Z_{in}\|_\infty \|\hat{\beta}_n(\omega) - \beta_n\|_1 \leq C_Z \cdot 1. \quad (47)$$

By assumption (23), we have $\sup_n \|\beta\|_1 < \infty$. Thus we consider the domain $\mathcal{X} \equiv [-C_Z(1 + \sup_n \|\beta_n\|_1), C_Z(1 + \sup_n \|\beta_n\|_1)]$ so that

$$|g^{(s)}(x) - g^{(s)}(y)| \leq \sup_{z \in \mathcal{X}} |g^{(s+1)}(z)| |x - y|, \quad \forall x, y \in \mathcal{X}. \quad (48)$$

By (47), we know $Z_{in}^\top(\omega) \hat{\beta}_n(\omega) \in \mathcal{X}$ for any $n \geq N(\omega)$ and almost every $\omega \in \Omega$. Similarly, $|Z_{in}^\top(\omega) \beta_n| \leq C_Z \|\beta_n\|_1$ implies $Z_{in}^\top(\omega) \beta_n \in \mathcal{X}$ for almost every ω . Then for almost every $\omega \in \Omega$ and large enough $N(\omega)$, applying (48) we have

$$\begin{aligned} \sup_i |g^{(s)}(Z_{in}^\top(\omega) \hat{\beta}_n(\omega)) - g^{(s)}(Z_{in}^\top(\omega) \beta_n)| &\leq \sup_{z \in \mathcal{X}} |g^{(s+1)}(z)| \sup_i |Z_{in}^\top(\omega) \hat{\beta}_n(\omega) - Z_{in}^\top(\omega) \beta_n| \\ &\leq \sup_{z \in \mathcal{X}} |g^{(s+1)}(z)| C_Z \|\hat{\beta}_n(\omega) - \beta_n\|_1. \end{aligned}$$

Thus we know $\sup_i |g^{(s)}(Z_{in}^\top(\omega) \hat{\beta}_n(\omega)) - g^{(s)}(Z_{in}^\top(\omega) \beta_n)| \rightarrow 0$ for almost every $\omega \in \Omega$.

Proof of (42): Inspired by (22), we define the event and the domain

$$\mathcal{E} \equiv \left\{ \sup_i |Z_{in}^\top \widehat{\beta}_n - Z_{in}^\top \beta_n| \leq 1 \right\}, \quad \mathcal{B} \equiv \left\{ x : |x| \leq C_Z \sup_n \|\beta_n\|_1 + 1 \right\}. \quad (49)$$

Then on the event \mathcal{E} , we know $|Z_{in}^\top \widehat{\beta}_n| \leq 1 + |Z_{in}^\top \beta_n| \leq 1 + C_Z \sup_n \|\beta_n\|_1$ so that $Z_{in}^\top \widehat{\beta}_n \in \mathcal{B}$ so does $Z_{in}^\top \beta_n$. Thus on the event \mathcal{E} ,

$$\begin{aligned} \sup_i |g^{(s)}(Z_{in}^\top \widehat{\beta}_n)| &\leq \sup_i |g^{(s)}(Z_{in}^\top \widehat{\beta}_n) - g^{(s)}(Z_{in}^\top \beta_n)| + \sup_i |g^{(s)}(Z_{in}^\top \beta_n)| \\ &\leq \sup_{a \in \mathcal{B}} |g^{(s+1)}(a)| \sup_i |Z_{in}^\top \widehat{\beta}_n - Z_{in}^\top \beta_n| + \sup_i |g^{(s)}(Z_{in}^\top \beta_n)| \\ &\leq \sup_{a \in \mathcal{B}} |g^{(s+1)}(a)| \sup_i \|Z_{in}\|_\infty \|\widehat{\beta}_n - \beta_n\|_1 + \sup_{a \in \mathcal{B}} |g^{(s)}(a)| \\ &\leq \sup_{a \in \mathcal{B}} |g^{(s+1)}(a)| C_Z \|\widehat{\beta}_n - \beta_n\|_1 + \sup_{a \in \mathcal{B}} |g^{(s)}(a)|. \end{aligned}$$

Since $\|\widehat{\beta}_n - \beta_n\|_1 = o_{\mathbb{P}}(1)$, it suffices to prove $\mathbb{P}[\mathcal{E}^c] \rightarrow 0$. In fact, by assumptions (20) and (22) in Lemma 2,

$$\sup_i |Z_{in}^\top (\widehat{\beta}_n - \beta_n)| \leq \|Z_{in}\|_\infty \|\widehat{\beta}_n - \beta_n\|_1 = o_{\mathbb{P}}(1).$$

Thus we have proved $\mathbb{P}[\mathcal{E}^c] \rightarrow 0$ so we have

$$\sup_i |g^{(s)}(Z_{in}^\top \widehat{\beta}_n)|^p = O_{\mathbb{P}}(1).$$

□

D.8 Proof of Lemma 15

Proof of Lemma 15. By the relationship between moments and cumulants as well as the relationship of the cumulant with the derivative of g in NEF, the moments $\mathbb{E}[|Y_{in}|^p | Z_{in}]$ for even p can be written as a polynomial of $g^{(s)}(Z_{in}^\top \beta_n)$, $s \in \mathbb{N}$. Also, we know $g^{(s)}(Z_{in}^\top \beta_n)$ are uniformly bounded due to assumption (20) and (23) so that we know the claim is true for Y_{in} and any even p . For the odd exponent, applying the Cauchy-Schwarz inequality also proves the claim, i.e., $\sup_n \mathbb{E}[|Y_{in}|^p] \leq \sqrt{\sup_n \mathbb{E}[|Y_{in}|^{2p}]} < \infty$. Similar proof works for X_{in} . □

E Additional figures and tables for simulation study

E.1 Additional figures for the simulation study

Figure 7-18 present the results of the simulation study for the Type-I error (as well as QQ-plots) and power with different values of θ . Figure 19-23 are scatter plots for comparing the null p-values of dCRT versus spaCRT when varying β and γ with different values of θ . Due to excessive consumption of memory, the displayed results are based on randomly sampled 20000 simulations among all 50000 simulations.

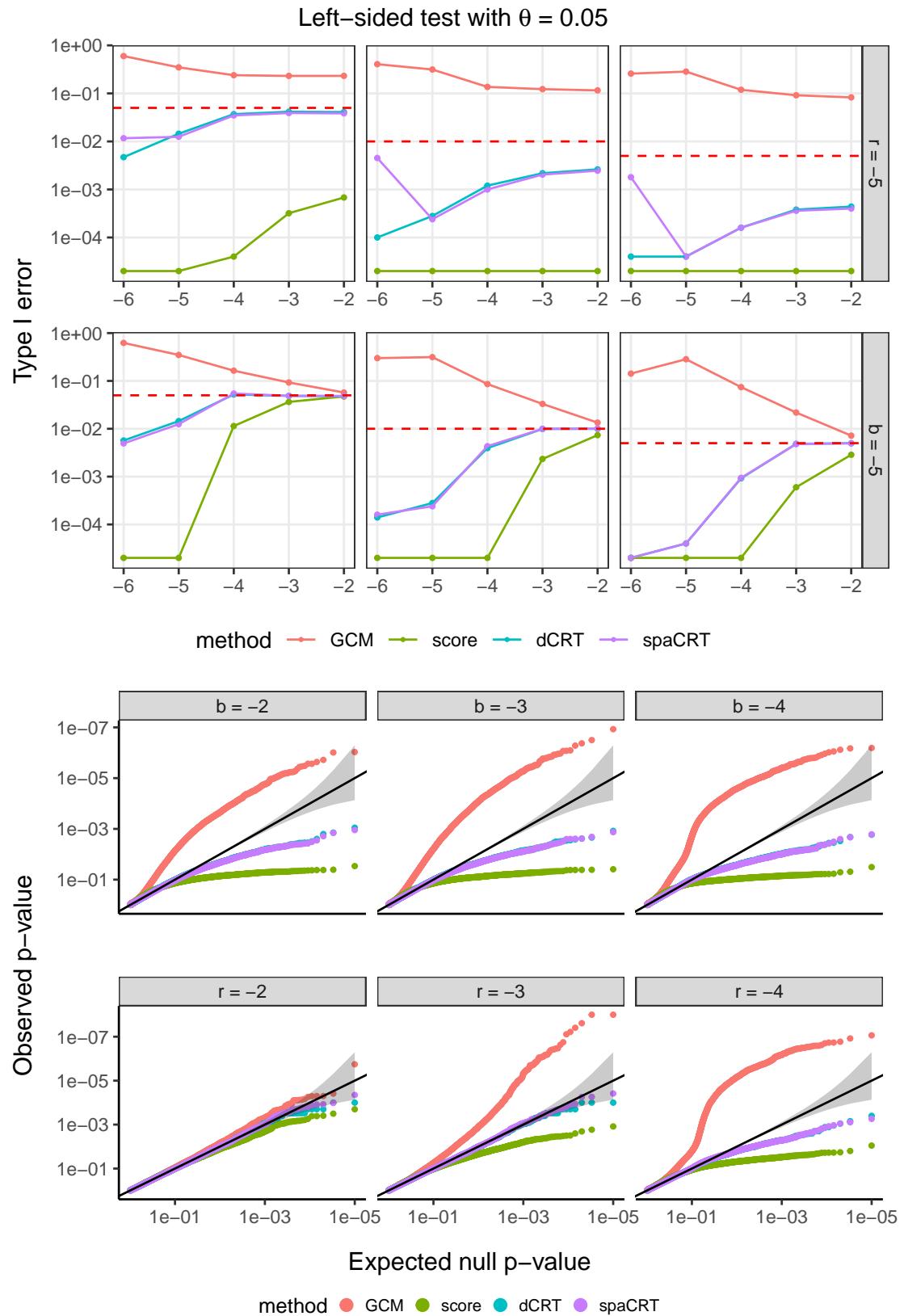


Figure 7: Type-I error plot and QQ-plots for the left-sided tests, with $\theta = 0.05$.

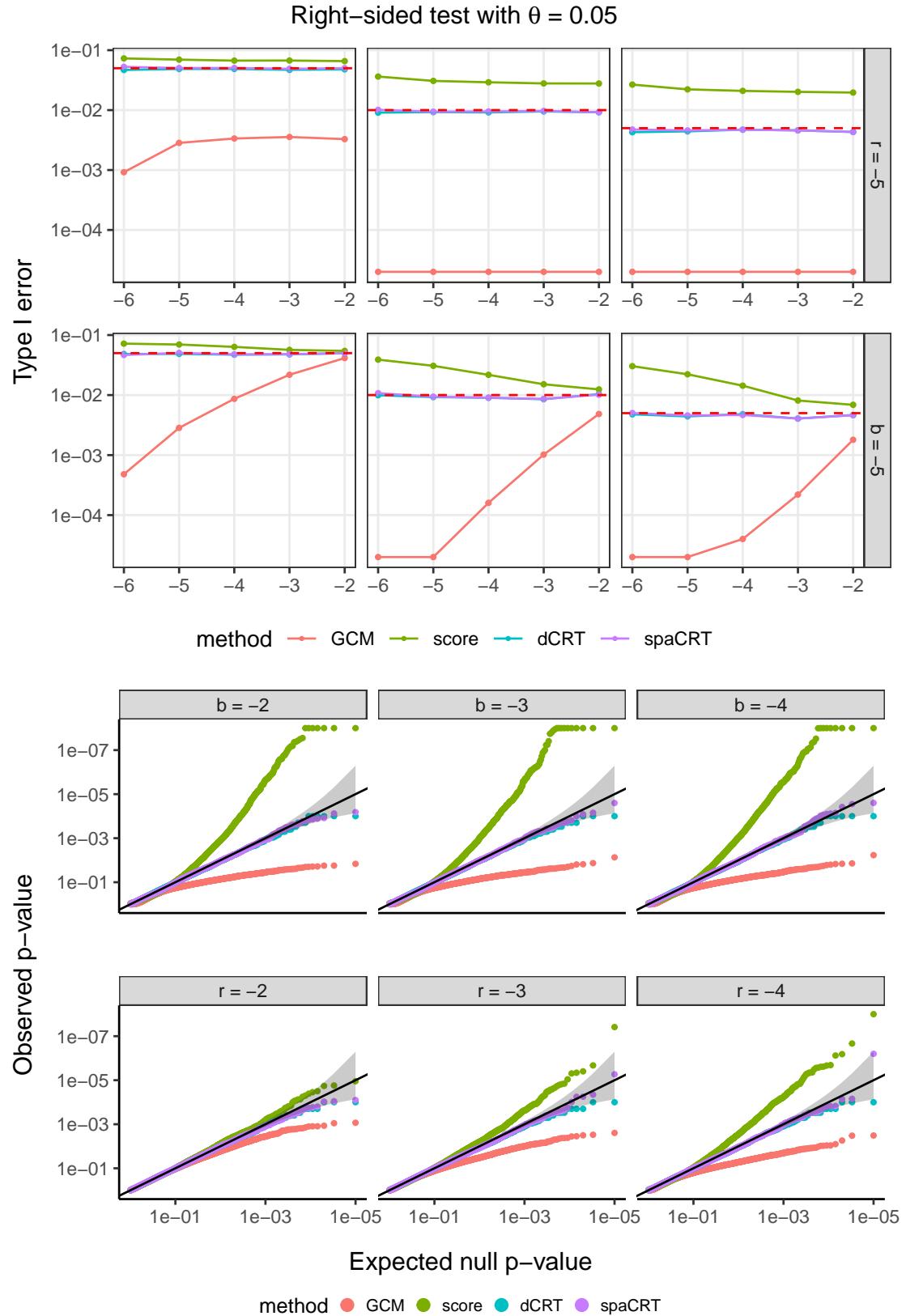


Figure 8: Type-I error and QQ-plots for the right-sided tests, with $\theta = 0.05$.

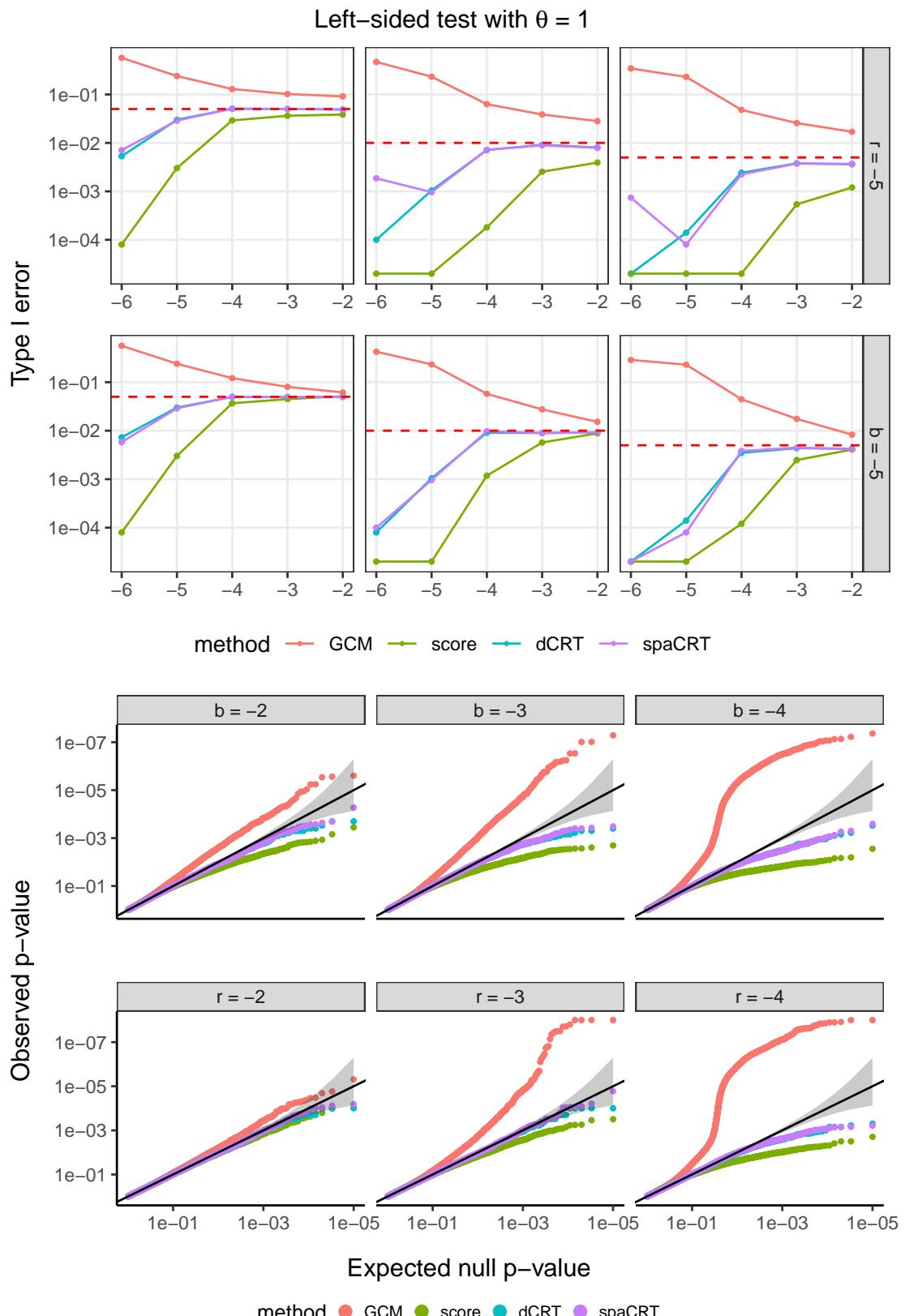


Figure 9: Type-I error and QQ-plots for the left-sided tests, with $\theta = 1$.

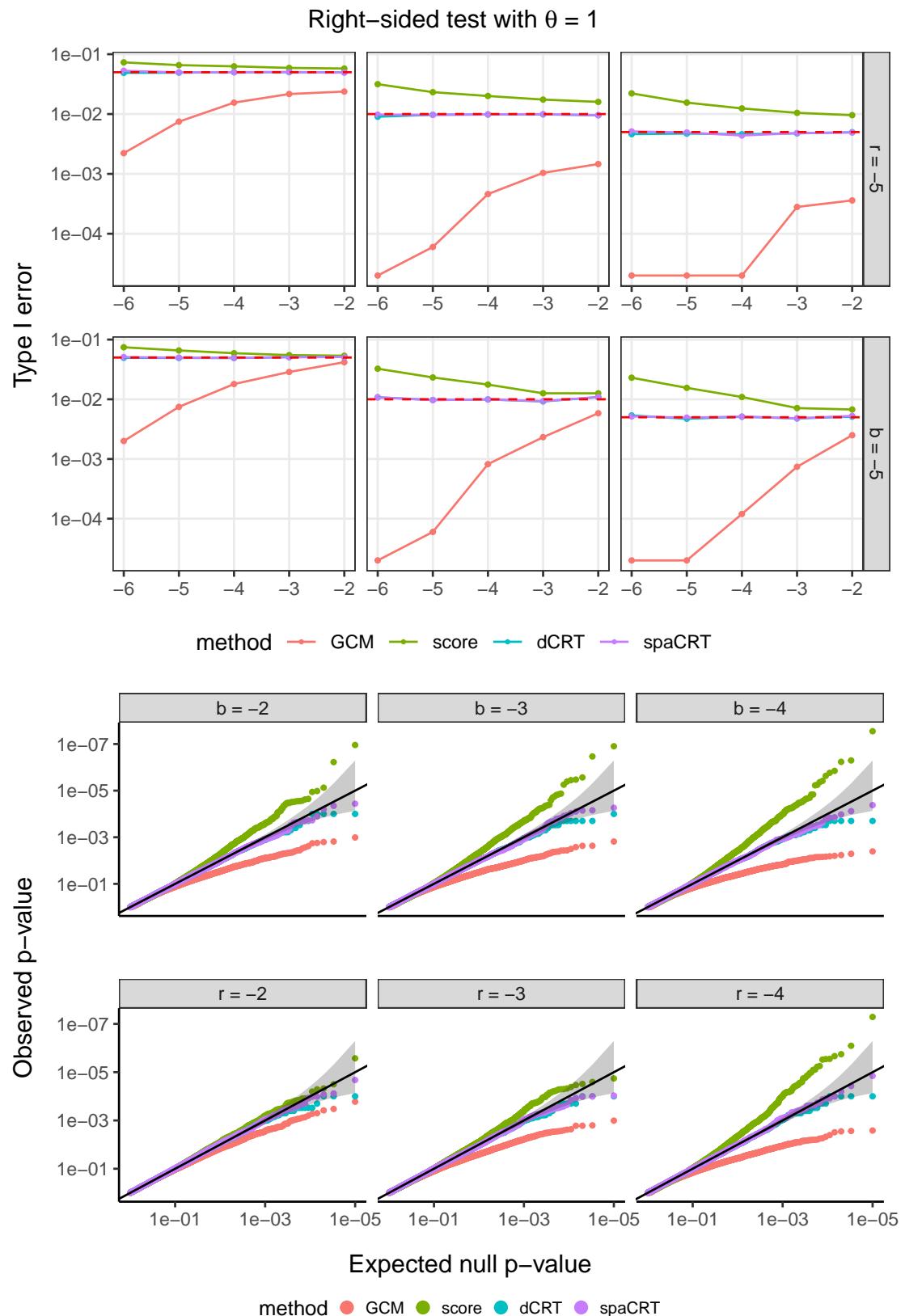


Figure 10: Type-I error and QQ-plots for the right-sided tests, with $\theta = 1$.

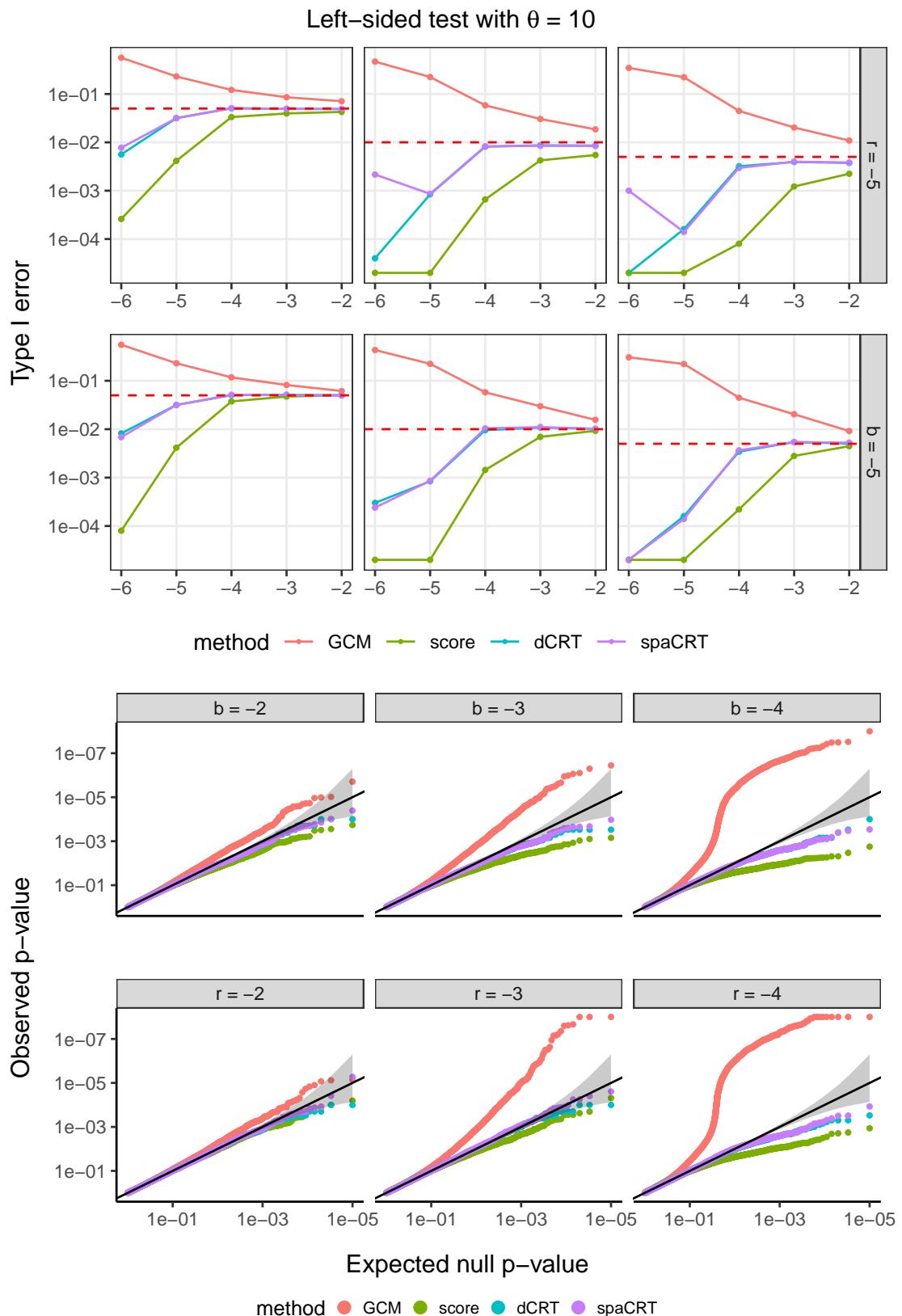


Figure 11: Type-I error and QQ-plots for the left-sided tests, with $\theta = 10$.

Right-sided test with $\theta = 10$

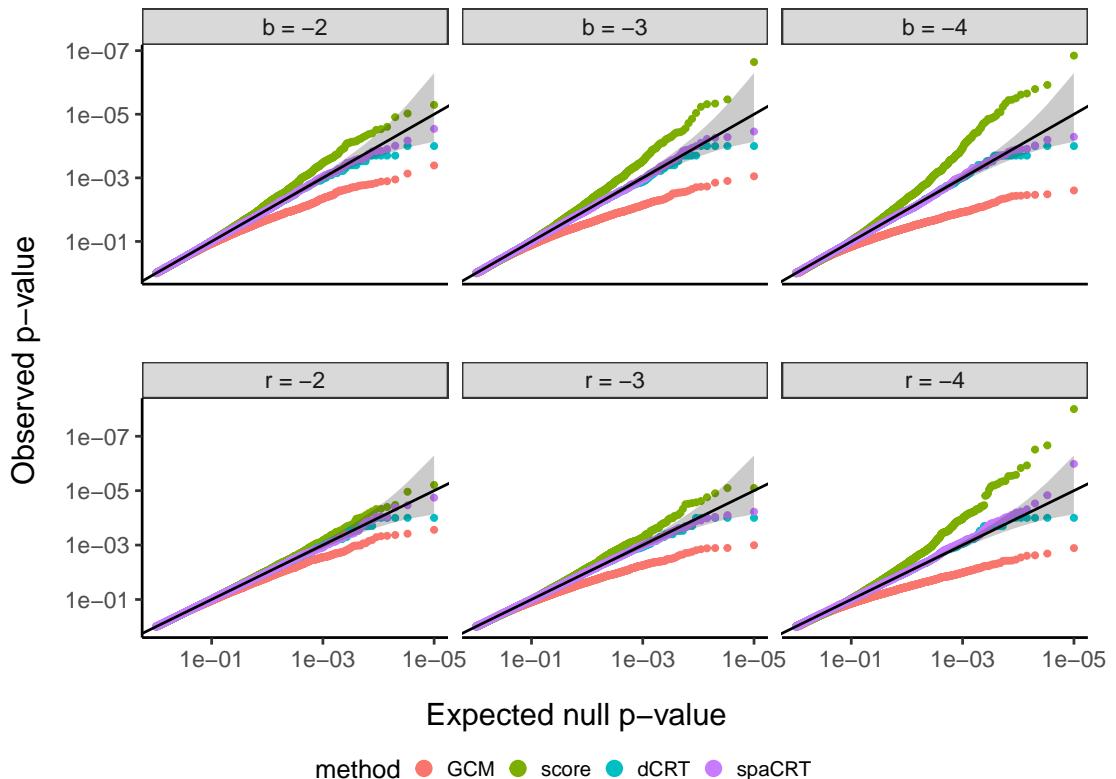
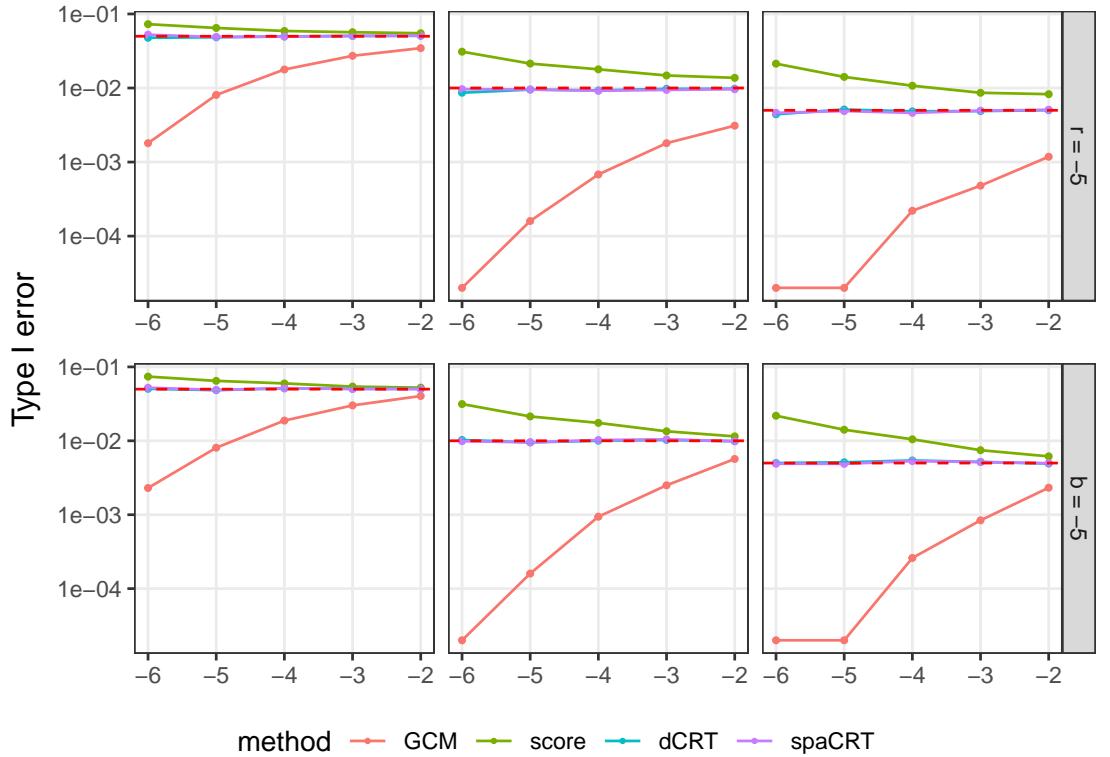


Figure 12: Type-I error and QQ-plots for the right-sided tests, with $\theta = 10$.

Left-sided test with $\theta = 0.05$

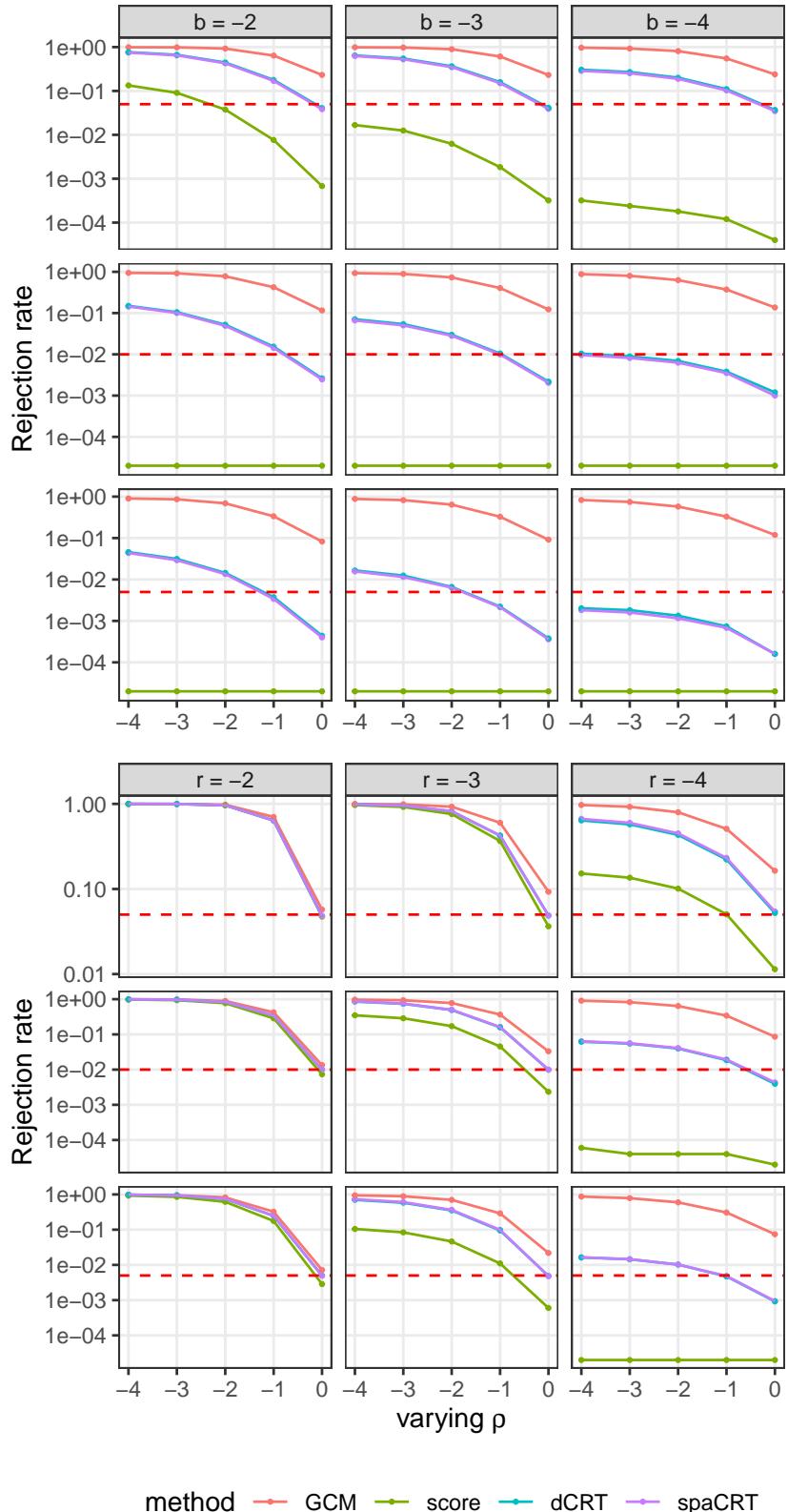


Figure 13: Power plots for the left-sided tests, with $\theta = 0.05$.

Right-sided test with $\theta = 0.05$

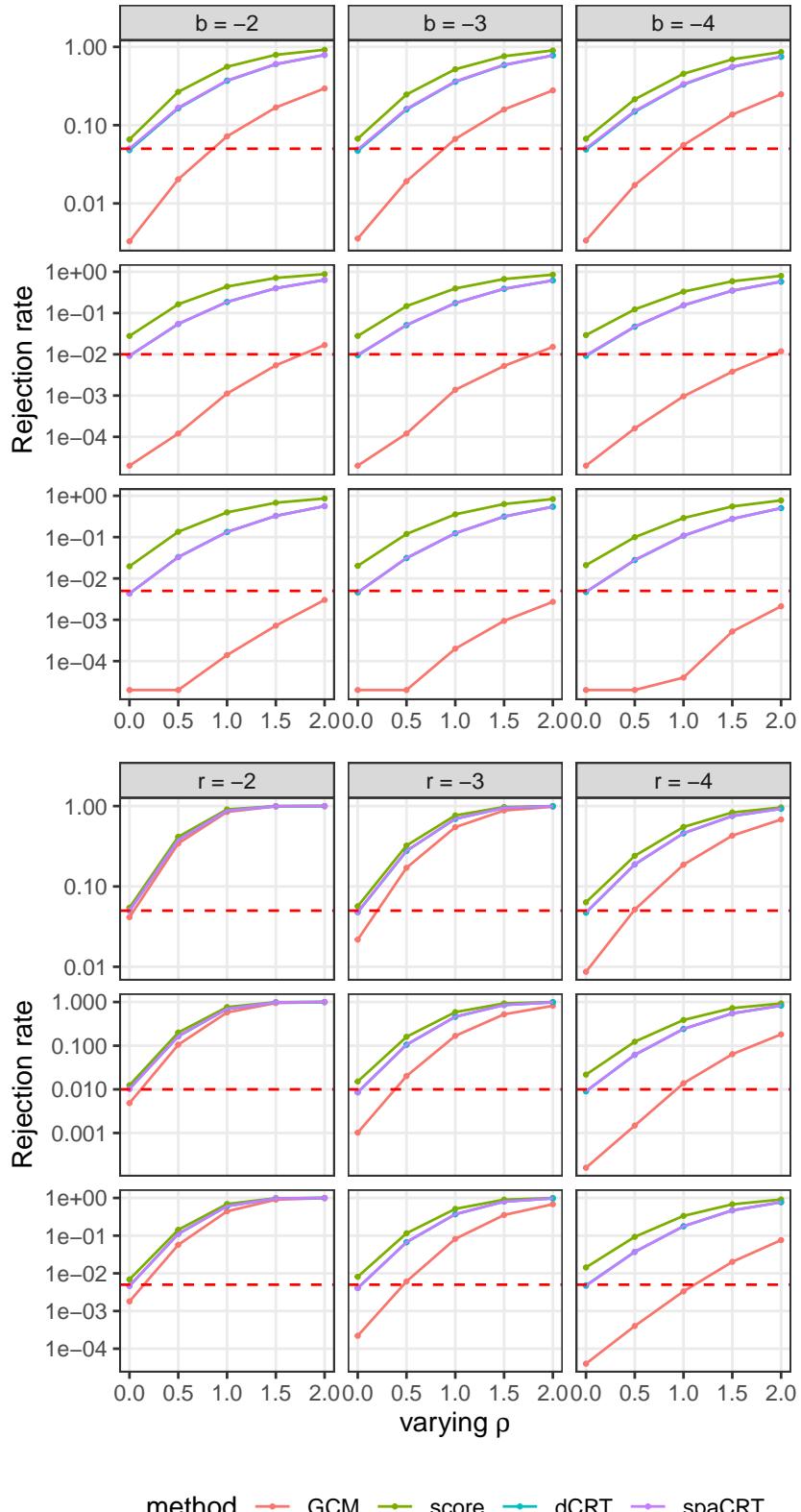


Figure 14: Power plots for the right-sided tests, with $\theta = 0.05$.

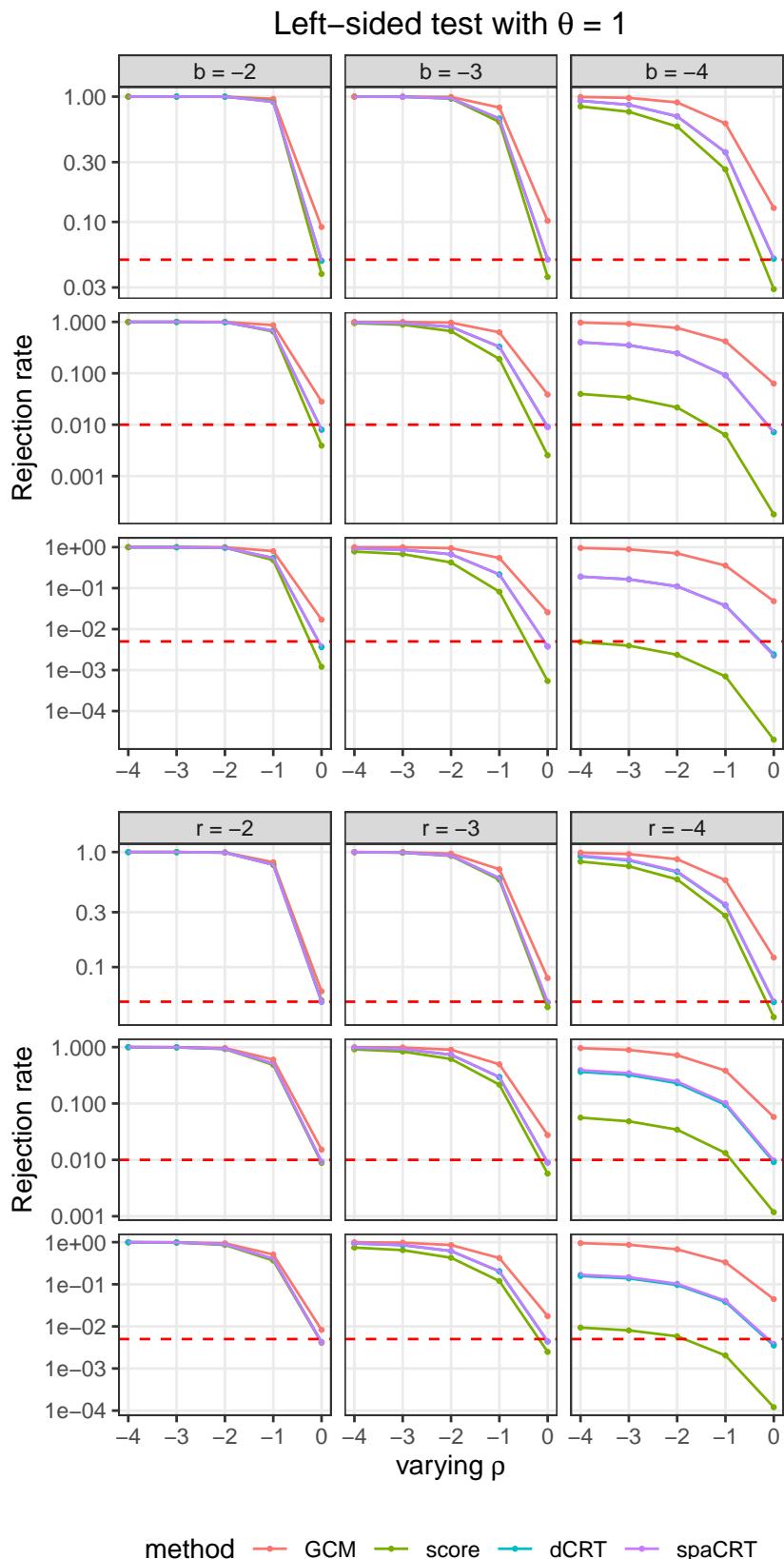


Figure 15: Power plots for the left-sided tests, with $\theta = 1$.

Right-sided test with $\theta = 1$

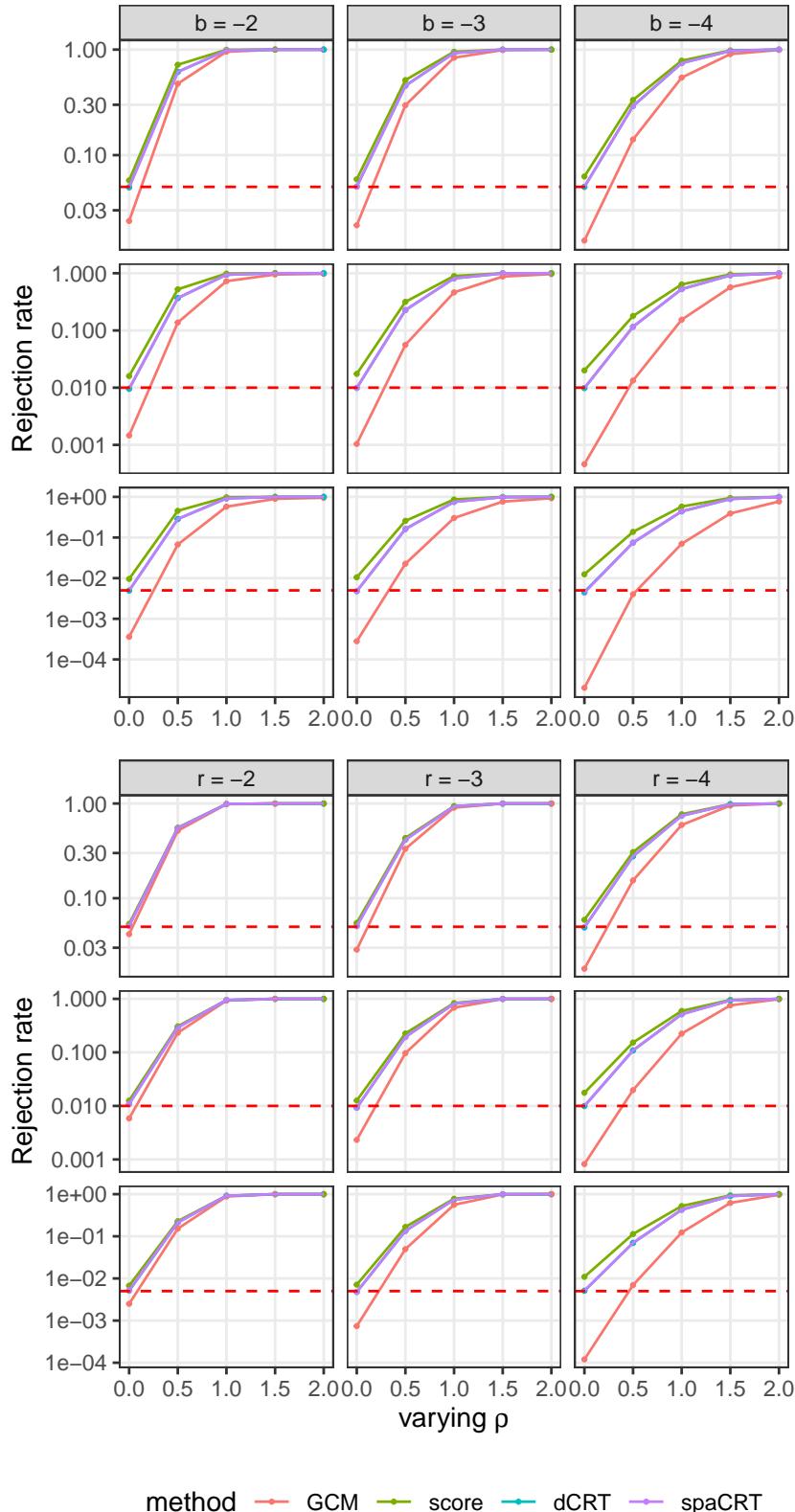


Figure 16: Power plots for the right-sided tests, with $\theta = 1$.

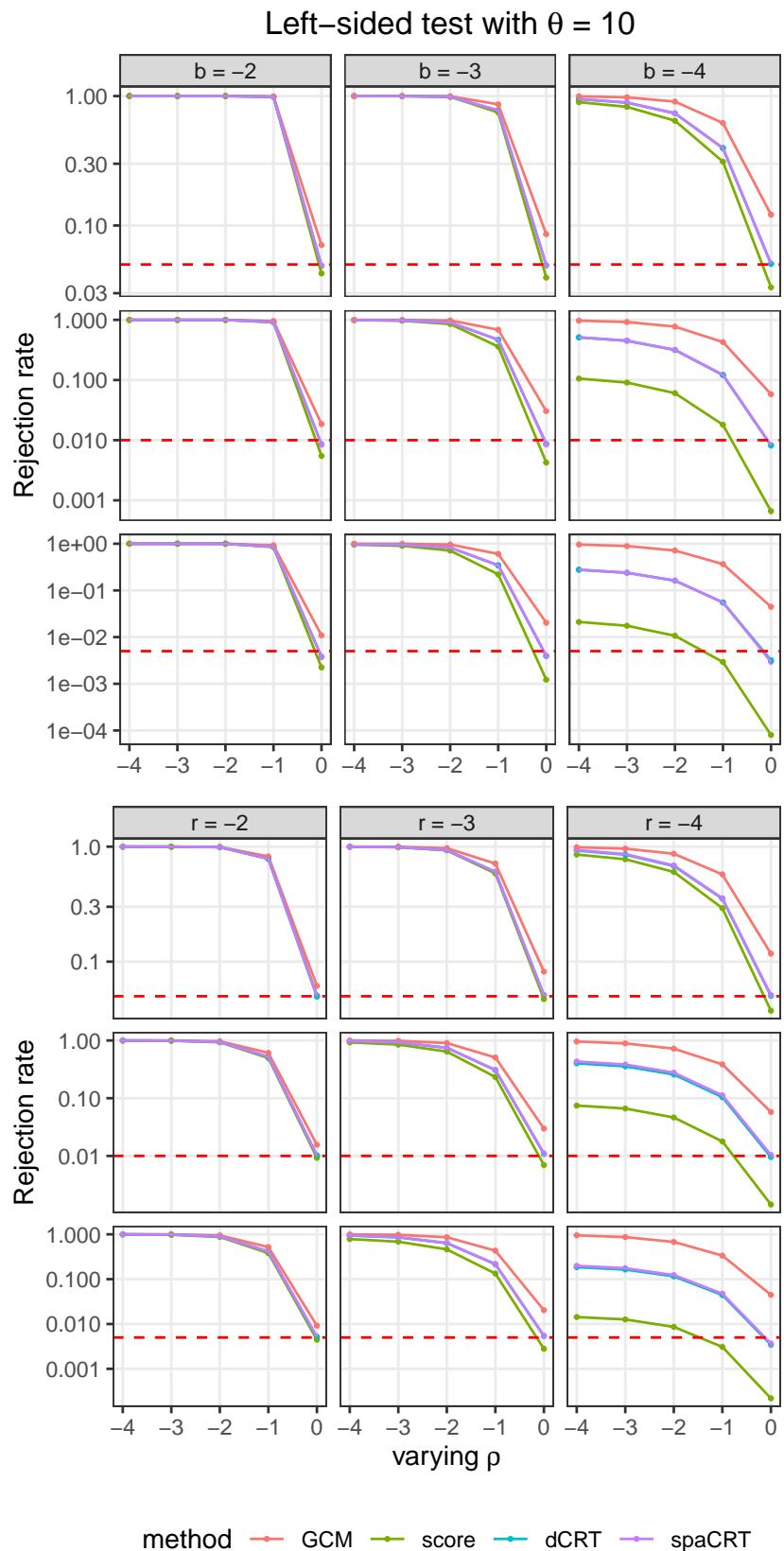


Figure 17: Power plots for the left-sided tests, with $\theta = 10$.

Right-sided test with $\theta = 10$

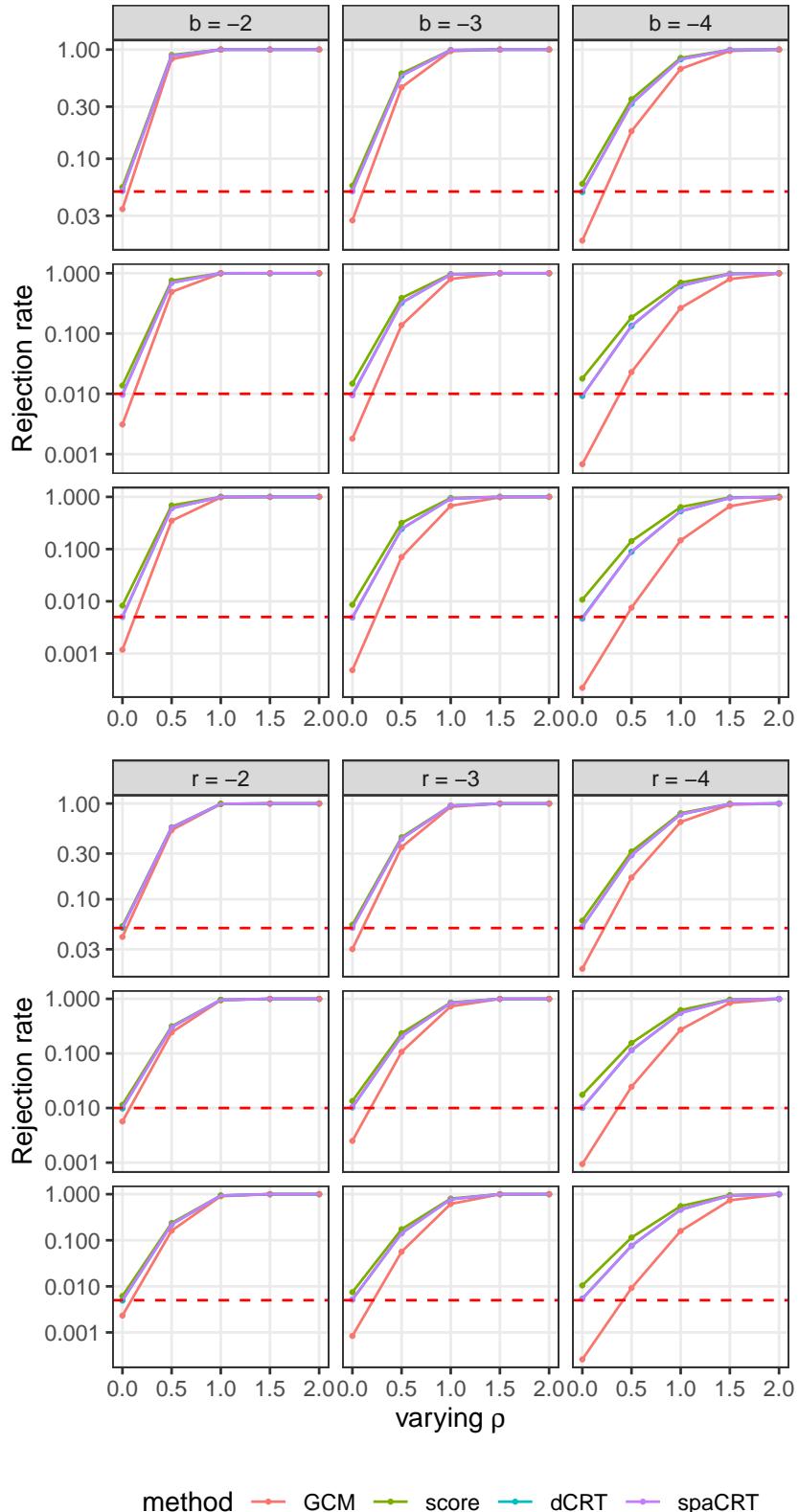


Figure 18: Power plots for the right-sided tests, with $\theta = 10$.

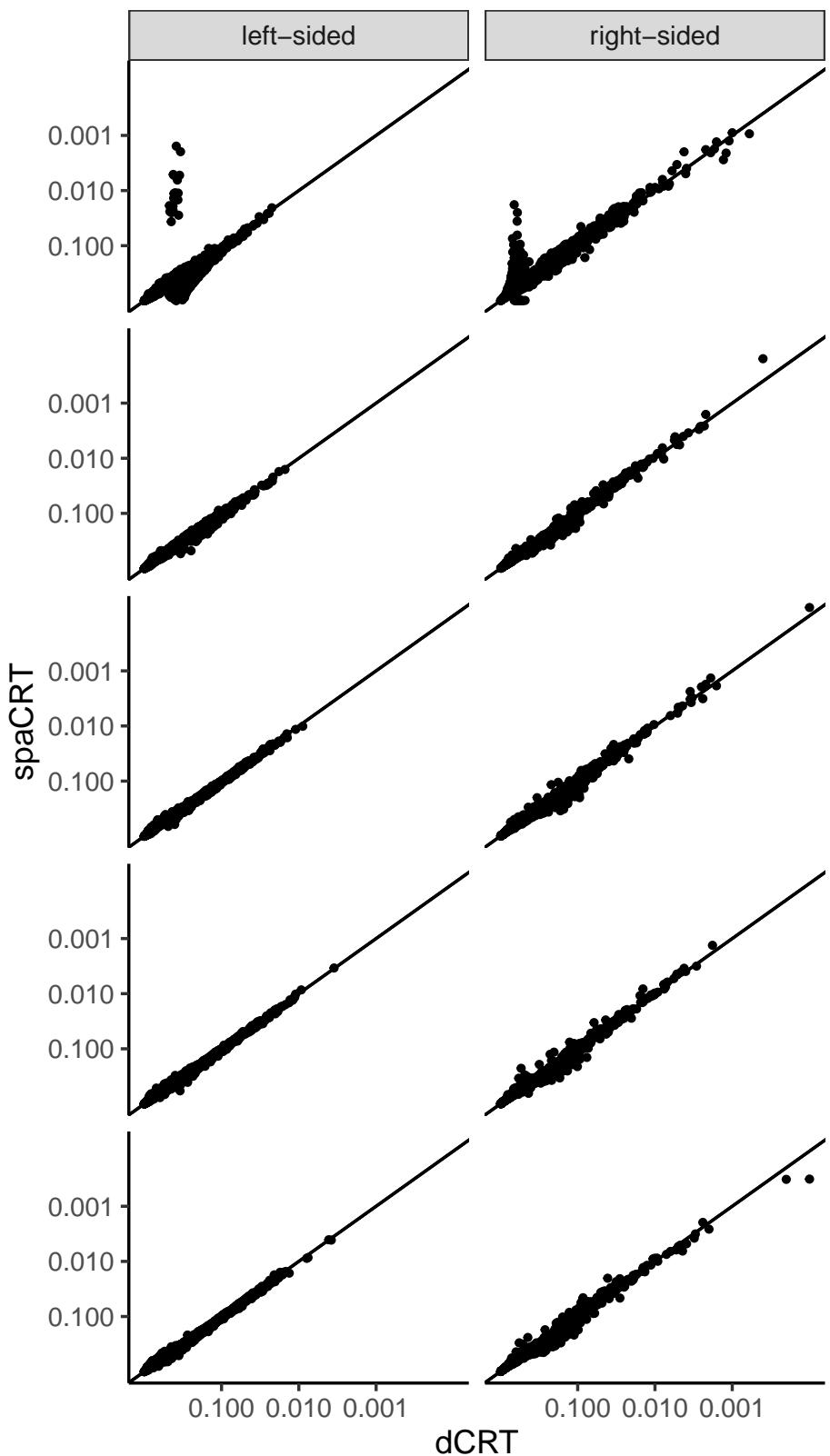


Figure 19: Scatter plots for the p -values of the left-sided and right-sided tests when varying $\beta_0 \in \{-6, -5, -4, -3, -2\}$ and fixing $\gamma_0 = -5$, with $\theta = 0.05$.

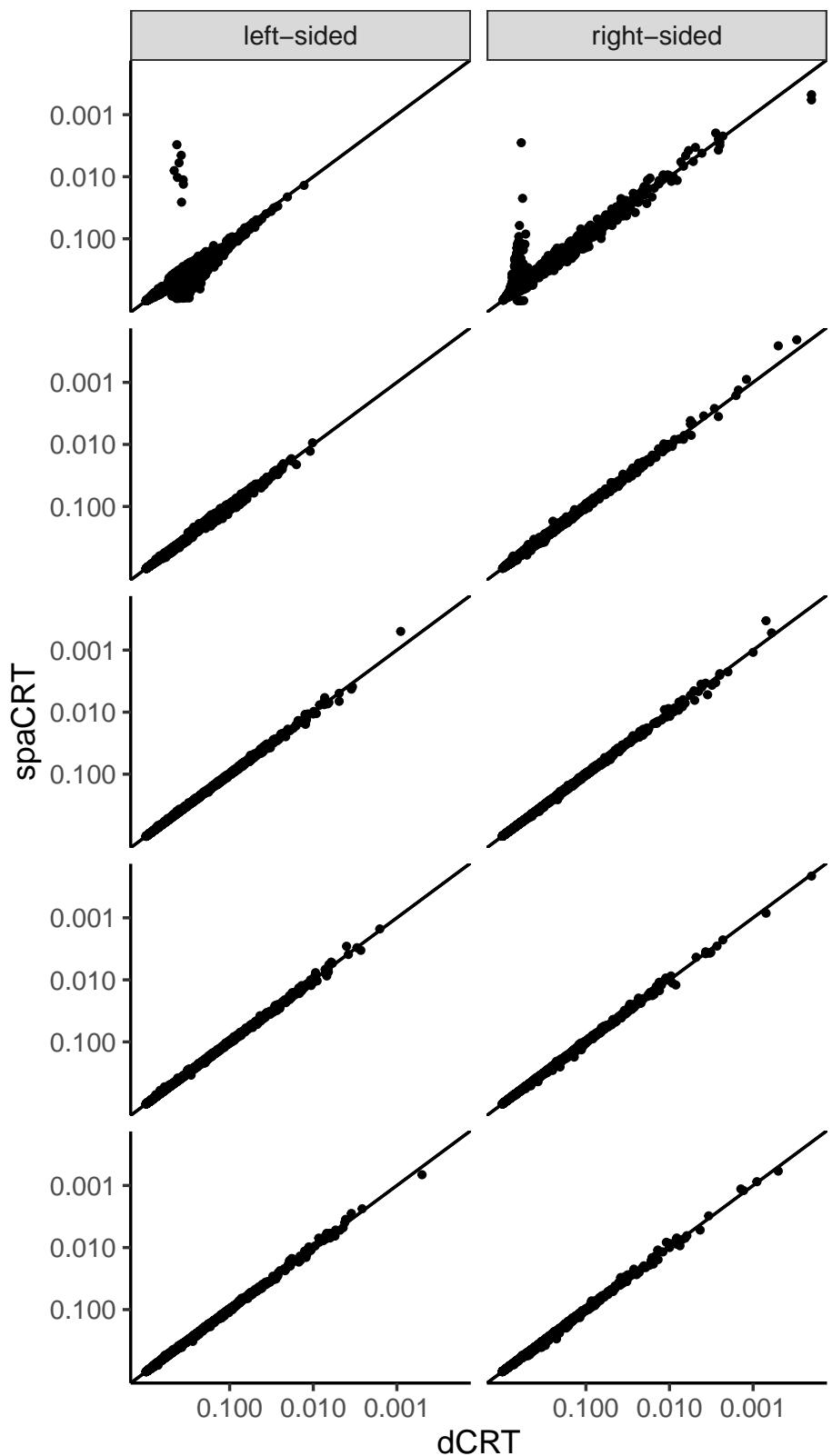


Figure 20: Scatter plots for the p -values of the left-sided and right-sided tests when varying $\beta_0 \in \{-6, -5, -4, -3, -2\}$ and fixing $\gamma_0 = -5$, with $\theta = 1$.

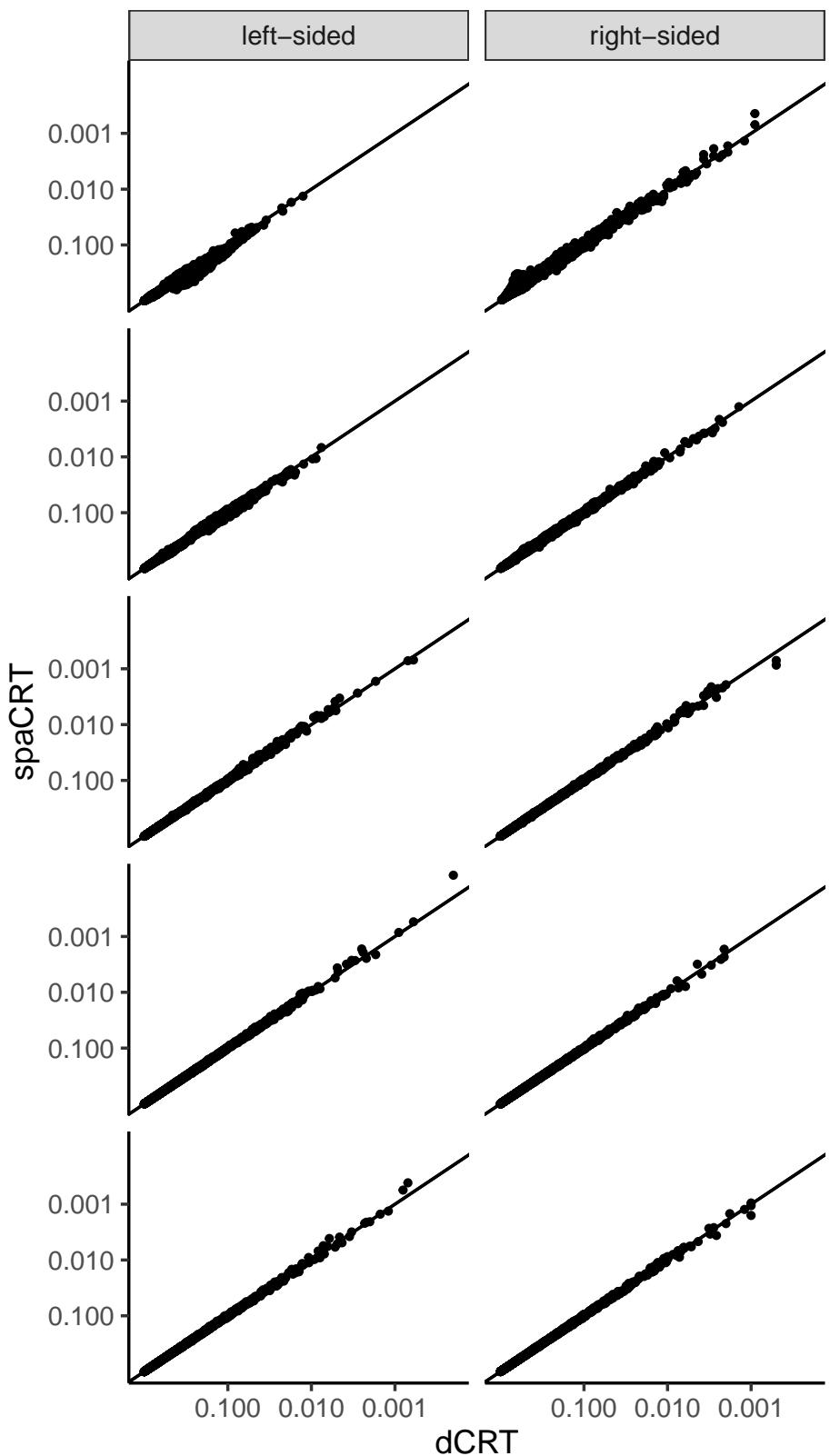


Figure 21: Scatter plots for the p -values of the left-sided and right-sided tests when varying $\gamma_0 \in \{-6, -5, -4, -3, -2\}$ and fixing $\beta_0 = -5$, with $\theta = 1$.

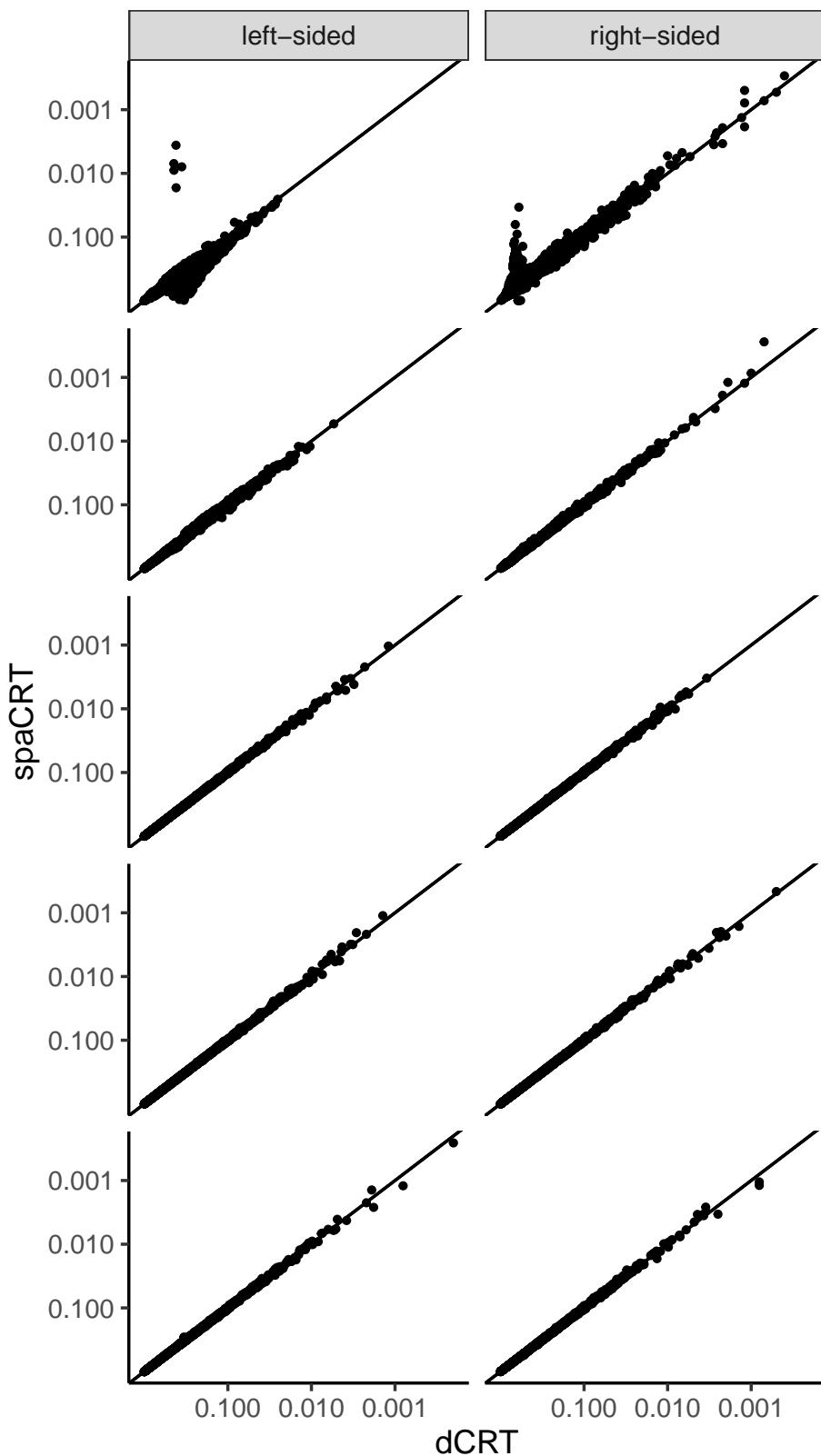


Figure 22: Scatter plots for the p -values of the left-sided and right-sided tests when varying $\beta_0 \in \{-6, -5, -4, -3, -2\}$ and fixing $\gamma_0 = -5$, with $\theta = 10$.

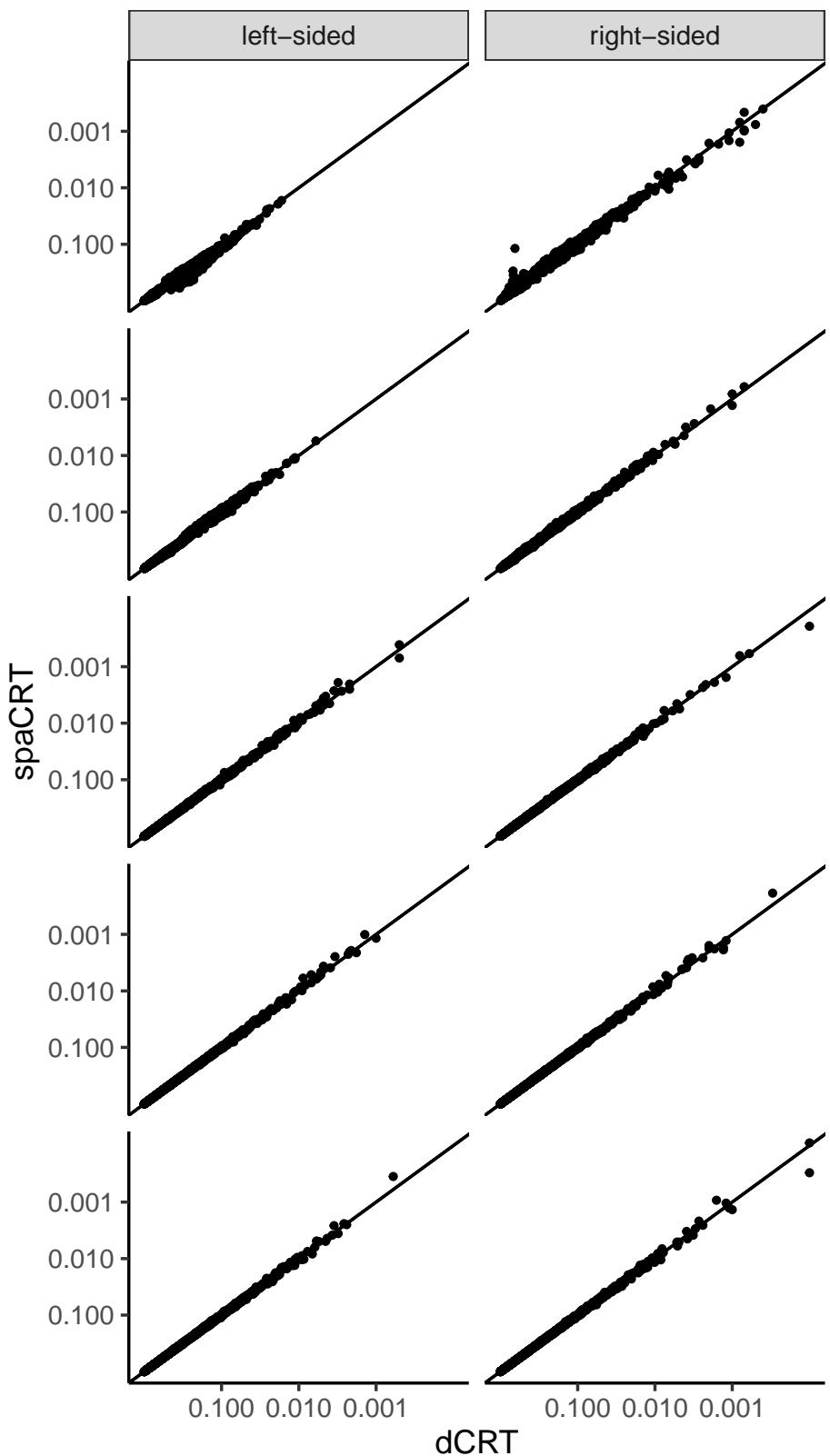


Figure 23: Scatter plots for the p -values of the left-sided and right-sided tests when varying $\gamma_0 \in \{-6, -5, -4, -3, -2\}$ and fixing $\beta_0 = -5$, with $\theta = 10$.

E.2 Additional tables for the simulation study

In this section, we compute the number of rejections by first applying the four single testing methods considered in section 4 and then applying either Bonferroni or Benjamini-Hochberg (BH) method to the obtained p -values. In order to do so, we regroup the 50000 replications to 50 independent simulation groups with each group including 5000 independent p -values. In particular, we only consider the null setup ($\rho = 0$) and $\theta = 0.05$. Thus we will expect the number of rejections will be very close to 0 after multiplicity correction and the final results are presented in the following tables.

Table 5: Number of rejections when $(\beta_0, \gamma_0, \rho) = (-6, -5, 0)$.

Method	Number of rejections			
	Left-sided test		Right-sided test	
	Bonferroni	BH	Bonferroni	BH
GCM test	0	607.6	0.0	0.0
Score test	0	0.0	5.6	17.8
dCRT	0	0.0	0.1	0.1
spaCRT	0	0.0	0.1	0.1

Table 6: Number of rejections when $(\beta_0, \gamma_0, \rho) = (-5, -6, 0)$.

Method	Number of rejections			
	Left-sided test		Right-sided test	
	Bonferroni	BH	Bonferroni	BH
GCM test	0	642.4	0.0	0.0
Score test	0	0.0	10.5	24.2
dCRT	0	0.0	0.1	0.1
spaCRT	0	0.0	0.0	0.1

Table 7: Number of rejections when $(\beta_0, \gamma_0, \rho) = (-5, -5, 0)$.

Method	Number of rejections			
	Left-sided test		Right-sided test	
	Bonferroni	BH	Bonferroni	BH
GCM test	19.2	343	0.0	0.0
Score test	0.0	0	4.5	11.9
dCRT	0.0	0	0.1	0.1
spaCRT	0.0	0	0.1	0.1

Table 8: Number of rejections when $(\beta_0, \gamma_0, \rho) = (-5, -4, 0)$.

Method	Number of rejections			
	Left-sided test		Right-sided test	
	Bonferroni	BH	Bonferroni	BH
GCM test	38.8	82	0.0	0.0
Score test	0.0	0	1.5	3.6
dCRT	0.0	0	0.1	0.1
spaCRT	0.0	0	0.1	0.1

Table 9: Number of rejections when $(\beta_0, \gamma_0, \rho) = (-5, -3, 0)$.

Method	Number of rejections			
	Left-sided test		Right-sided test	
	Bonferroni	BH	Bonferroni	BH
GCM test	3.0	8.8	0.0	0.0
Score test	0.0	0.0	0.5	0.9
dCRT	0.1	0.1	0.0	0.1
spaCRT	0.1	0.1	0.1	0.1

Table 10: Number of rejections when $(\beta_0, \gamma_0, \rho) = (-5, -2, 0)$.

Method	Number of rejections			
	Left-sided test		Right-sided test	
	Bonferroni	BH	Bonferroni	BH
GCM test	0.2	0.3	0.0	0.0
Score test	0.0	0.0	0.2	0.3
dCRT	0.0	0.1	0.1	0.1
spaCRT	0.0	0.0	0.1	0.1

Table 11: Number of rejections when $(\beta_0, \gamma_0, \rho) = (-4, -5, 0)$.

Method	Number of rejections			
	Left-sided test		Right-sided test	
	Bonferroni	BH	Bonferroni	BH
GCM test	30.8	154.1	0.0	0.0
Score test	0.0	0.0	4.2	11.1
dCRT	0.0	0.0	0.1	0.1
spaCRT	0.0	0.0	0.2	0.2

Table 12: Number of rejections when $(\beta_0, \gamma_0, \rho) = (-3, -5, 0)$.

Method	Number of rejections			
	Left-sided test		Right-sided test	
	Bonferroni	BH	Bonferroni	BH
GCM test	11.3	142	0.0	0.0
Score test	0.0	0	3.9	10.5
dCRT	0.0	0	0.1	0.1
spaCRT	0.0	0	0.1	0.1

Table 13: Number of rejections when $(\beta_0, \gamma_0, \rho) = (-2, -5, 0)$.

Method	Number of rejections			
	Left-sided test		Right-sided test	
	Bonferroni	BH	Bonferroni	BH
GCM test	5.1	130.6	0.0	0.0
Score test	0.0	0.0	3.6	9.1
dCRT	0.0	0.0	0.1	0.1
spaCRT	0.0	0.0	0.0	0.0

F Additional figures and tables for real data analysis

In section F.1, we present additional figures for real data analysis including QQ-plots faceting across different effective sample size (Figure 24) and QQ-plots faceting across different dispersion parameters (Figure 25). In section F.2, we show a table including the number of rejections when applying Bonferroni or BH method to the pairs involving the non-targeting perturbations (thus under the null). The total number of hypotheses is 153000.

F.1 Additional figures for the real data analysis

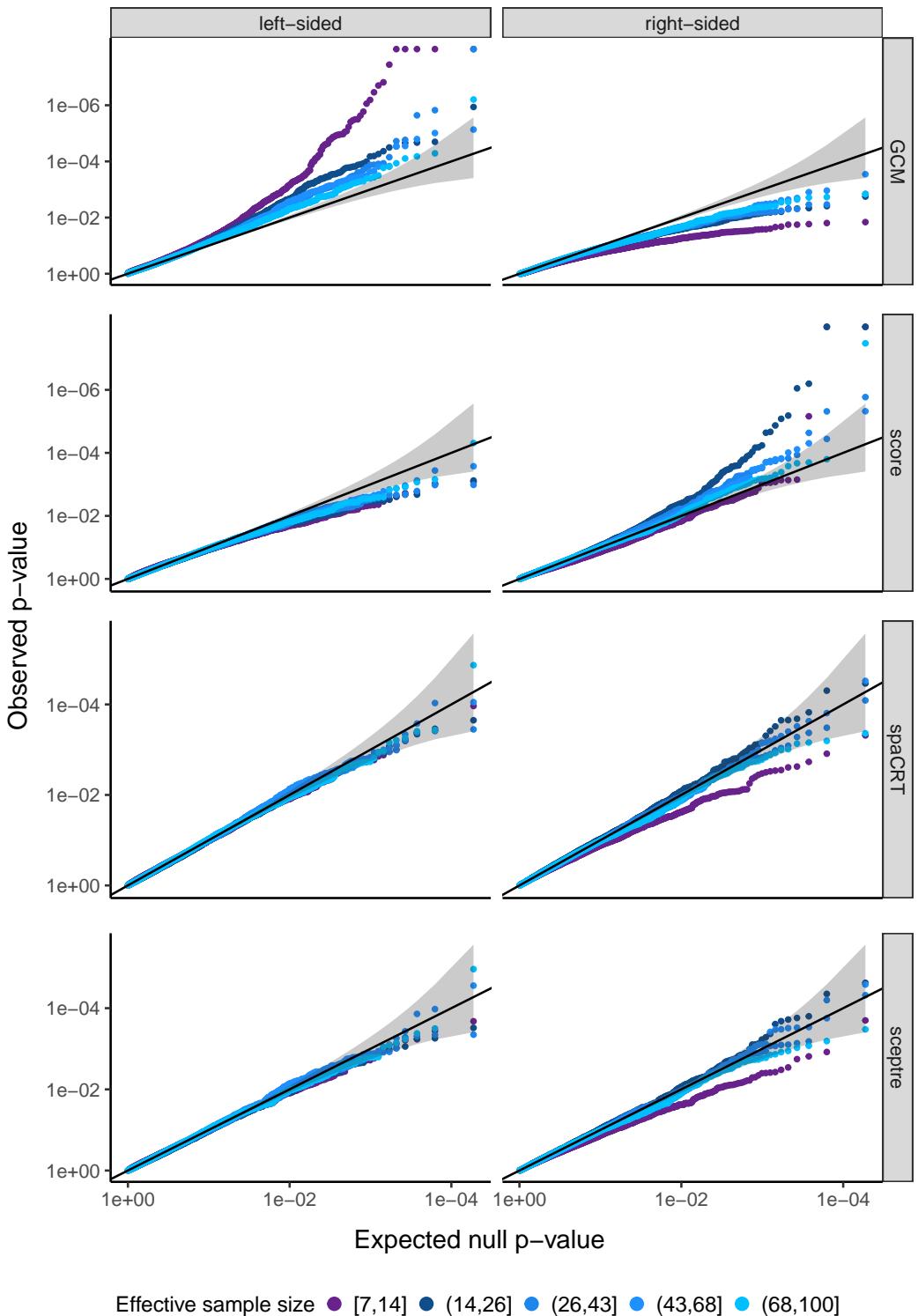


Figure 24: QQ-plots for the p -values of right-sided test from different methods under low effective sample size.

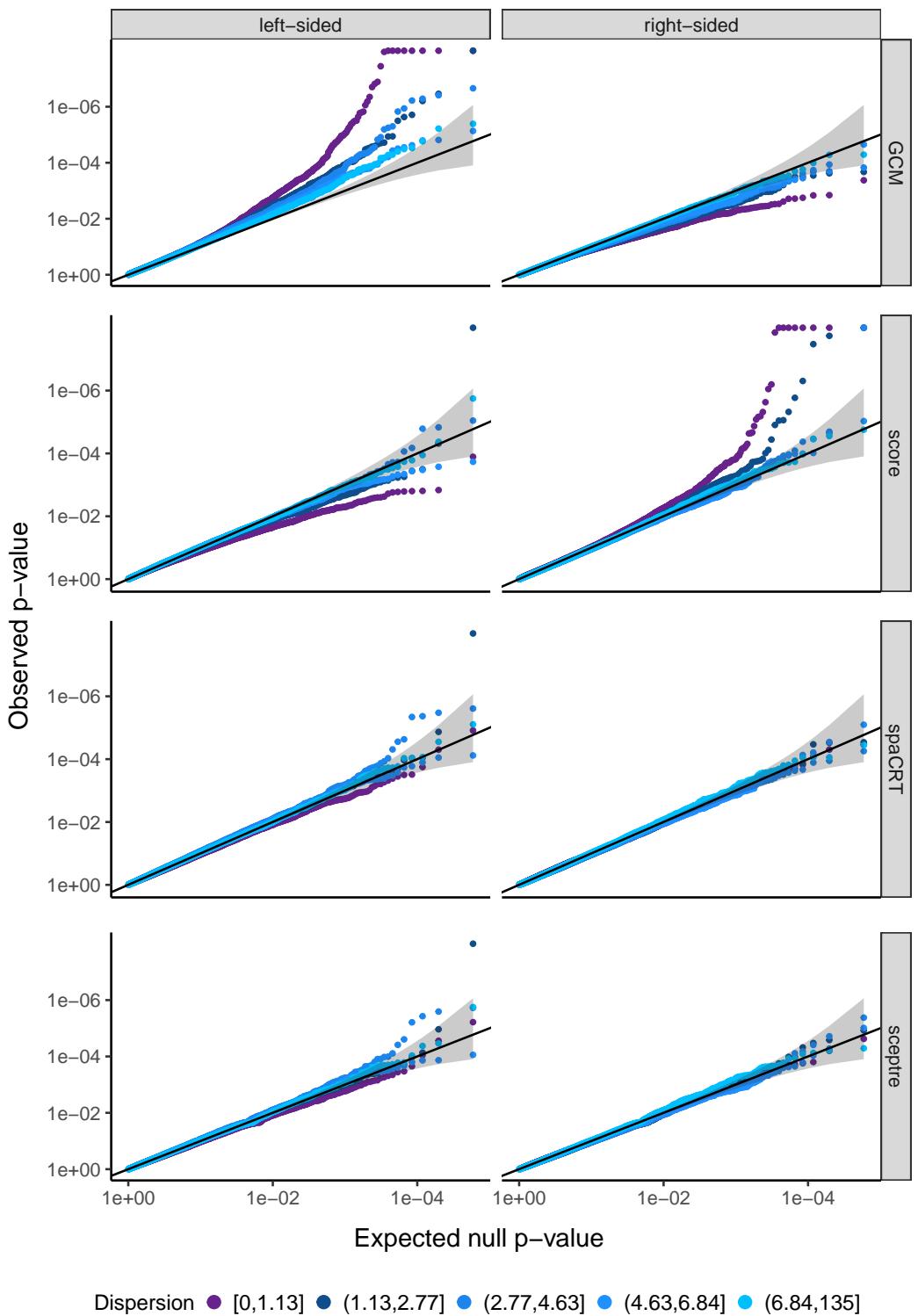


Figure 25: QQ-plots for the p -values of left-sided test from different methods stratified by dispersion parameter.

F.2 Additional tables for the real data analysis

Table 14: Number of rejections for negative control pairs on the Gasperini data.

Method	Number of rejections			
	Left-sided test		Right-sided test	
	Bonferroni	BH	Bonferroni	BH
GCM test	22	128	0	0
Score test	1	1	15	29
spaCRT	1	1	0	0
dCRT	1	4	0	0