Fisher-Pitman permutation tests based on nonparametric Poisson mixtures with application to single cell genomics

Zhen Miao^{*}, Weihao Kong[†], Ramya Korlakai Vinayak[‡], Wei Sun[§], and Fang Han[¶]
June 8, 2021

Abstract

This paper investigates the theoretical and empirical performance of Fisher-Pitman-type permutation tests for assessing the equality of unknown Poisson mixture distributions. Building on nonparametric maximum likelihood estimators (NPMLEs) of the mixing distribution, these tests are theoretically shown to be able to adapt to complicated unspecified structures of count data and also consistent against their corresponding ANOVA-type alternatives; the latter is a result in parallel to classic claims made by Robinson (Robinson, 1973). The studied methods are then applied to a single-cell RNA-seq data obtained from different cell types from brain samples of autism subjects and healthy controls; empirically, they unveil genes that are differentially expressed between autism and control subjects yet are missed using common tests. For justifying their use, rate optimality of NPMLEs is also established in settings similar to nonparametric Gaussian (Wu and Yang, 2020a) and binomial mixtures (Tian et al., 2017; Vinayak et al., 2019).

Keywords: Fisher-Pitman permutation tests, nonparametric MLE, nonparametric Poisson mixture, single-cell genomics, minimax risk

1 Introduction

Considering an experiment with multiple samples drawn from multiple populations, distinguishing possible difference among them in one or more dimensions is a fundamental statistical task. In the classical test of the null hypothesis of no mean differences, one-way analysis of variance (ANOVA, cf. Fisher (1925)) F-test is perhaps the most commonly used tool, and is the uniformly most powerful invariant one under additional normal assumption, c.f. Scheffé (1959, page 50).

Despite its popularity, one-way ANOVA has its competing alternatives. In the context of randomized experiments, Fisher (Fisher, 1935) initialized an ingenious permutation approach as an alternative to performing ANOVA F-test. This idea was later developed further by Pitman (Pitman,

^{*}Department of Statistics, University of Washington, Seattle; e-mail: zhenm@uw.edu

[†]Google Inc; e-mail: kweihao@gmail.com

[‡]Department of Electrical and Computer Engineering, University of Wisconsin-Madison; e-mail: ramya@ece.wisc.edu

[§]Public Health Science Division, Fred Hutchinson Cancer Research Center; e-mail: wsun@fredhutch.org

[¶]Department of Statistics, University of Washington, Seattle; e-mail: fanghan@uw.edu

1938). The resulting procedures, often termed the Fisher-Pitman permutation tests in literature, achieve the appealing property of being exactly distribution-free and have been suggested in various contexts as, e.g., when the distributional assumptions of F-tests no longer hold (Marascuilo and McSweeney, 1977; Still and White, 1981; Berry and Mielke, 1983). Robustness properties have been further studied empirically (Boik, 1987) and theoretically (Chung and Romano, 2013); power analyses were also performed in Hoeffding (1952) and Robinson (1973).

Although being originally defined in Euclidean spaces, it is by now well understood that the ANOVA F-tests and especially their permutation-type alternatives are able to adapt to an arbitrary metric space. This is via the approach of "interpoint" distance functions (Mielke Jr et al., 1976; Mielke Jr, 1984) that uses an alternative representation of the F statistic as a function of betweenand within-group pairwise distances. Thus, through replacing the original Euclidean distance by any properly defined distance function, the idea of Fisher-Pitman permutation tests is now implementable in many complicated metric spaces beyond the Euclidean (Anderson, 2001; Mielke and Berry, 2007; Petersen and Müller, 2019).

Our study of Fisher-Pitman-type permutation tests stems from the analysis of single-cell RNAseq (scRNA-seq) data, and particularly, a framework that was recently promoted in Sarkar and Stephens (2021). There, the authors described how a separation of measurement and expression models is able to clarify confusion in modeling scRNA-seq data, and accordingly advocated using the terminology of Poisson mixtures to unify many existing models (cf. Table 1 in Sarkar and Stephens (2021)). In detail, thinking about $X_{ij}^{(k)}$ to be the absolute expression of a specific general in cell $i \in [N_{jk}] := \{1, 2, \dots, N_{jk}\}$ of subject $j \in [n_k]$ of population $k \in [K]$, we are interested in studying the following model of $X_{ij}^{(k)}$ that is a slight simplification to Sarkar and Stephens's Equation (1):

$$X_{ij}^{(k)} \mid \lambda_{ij}^{(k)} \sim \text{Poisson}(r_{ij}^{(k)}\lambda_{ij}^{(k)});$$
 (measurement model) (1.1)
$$\lambda_{ij}^{(k)} \sim Q_j^{(k)}.$$
 (expression model) (1.2)

$$\lambda_{ij}^{(k)} \sim Q_j^{(k)}$$
. (expression model) (1.2)

Here $r_{ij}^{(k)} > 0$ adjusts the cell "read depth" (cf. Zhang et al. (2020, Page 1)) and in this paper is assumed to be known; $Q_j^{(k)}$ is a properly defined distribution that describes the "expression level" of the gene in population k and is assumed to have a compact support on the nonnegative real line. Adopting the statistical terminology, for each $k \in [K]$ and $j \in [n_k]$, $\{X_{ij}^{(k)}, i = 1, \dots, N_{jk}\}$ then independently follow Poisson mixture distributions of point mass functions (PMFs)

$$h_{ij}^{(k)}(x) := \int_0^\infty e^{-\lambda r_{ij}^{(k)}} \frac{\{\lambda r_{ij}^{(k)}\}^x}{x!} \mathrm{d}Q_j^{(k)}(\lambda), \quad x = 0, 1, 2, \dots$$

and a mixing distribution $Q_j^{(k)}$ that has to be characterized by a nonparametric model; see Sarkar and Stephens (2021, Section "Modeling scRNA-seq data") for a discussion of why a nonparametric model of $Q_i^{(k)}$ is preferred in single-cell genomics, though Sarkar and Stephens (2021) did not employ such Poisson mixtures for individual level differential expression testing, which however is the main focus of this work.

Based on the observations $\left\{X_{ij}^{(k)}, i \in [N_{jk}], j \in [n_k], k \in [K]\right\}$ as well as the measure/expression models (1.1)-(1.2), a natural question to ask is whether there exists any population-level gene expression difference among the K groups. For this, we propose to leverage a Fisher-Pitman-type permutation test based on consistent estimators $\{\widetilde{Q}_j^{(k)}, j \in [n_k], k \in [K]\}$ of the mixing distributions $\{Q_j^{(k)}, j \in [n_k], k \in [K]\}$ under Wasserstein metrics, which have received much attention in recent mixture distribution estimation literature (see, among many others, Nguyen et al. (2013), Tian et al. (2017), Vinayak et al. (2019), Wu and Yang (2020a), and the references therein). Particularly appealing choices to us include the NPMLE $\widehat{Q}_j^{(k)}$ and its Poisson-smoothed one $h_{\widehat{Q}_j^{(k)}}$ (notation to be introduced by the end of this section); see Section 2 ahead for the detailed description of the testing procedure.

Many methods have been developed for differential expression analysis of scRNA-seq data (Chen et al., 2019). However, their focus is differential expression between two groups of cells instead of two groups of individuals. For individual level testing, a standard approach is to add up gene expression across all the cells (of a particular cell type) of an individual to create a pseudo-bulk sample, and then apply the methods for differential expression analysis using bulk RNA-seq data, such as DESeq2 (Love et al., 2014). The novelty of our proposed procedure is that we assess differential expression across individuals using cell level data instead of pseudo-bulk data. Furthermore, the proposed tests are shown to be consistent against their ANOVA-type alternatives, i.e., they are able to asymptotically distinguish the null from any fixed alternative where the "between-group" variation is larger than the "within-group" variation, a result that sheds insight to the power of the developed tests and is in line with classic observations (Hoeffding, 1952; Robinson, 1973)¹.

As a byproduct of our theoretical study, this paper further justifies the use of NPMLEs via establishing their rate-optimality in estimating the Poisson mixing distribution under the Wasserstein-1 (W_1) metric. Although the consistency of the NPMLEs has been established in the literature for different nonparametric mixture models (cf. Simar (1976) for nonparametric Poisson mixtures; and Chen (2017) and the references therein for more general models), NPMLEs' rates of convergence and their matching to a minimax lower bound are long standing until very recently. Built on the breakthroughs in binomial (Tian et al., 2017; Vinayak et al., 2019) and Gaussian mixtures (Wu and Yang, 2020a) (see also Jiang and Zhang (2019) for a related study on the nonparametric likelihood ratio test) as well as the new analytical techniques devised in Jiao et al. (2015), Wu and Yang (2016), Jiao et al. (2018), and Han and Shiragur (2020), we are now able to further the optimality of NPMLEs to the nonparametric Poisson mixtures under minimal assumptions on the true mixing distribution function. These results yield additional theoretical support for the use of NPMLEs in our developed tests.

The rest of this paper is organized as follows. Section 2 describes the model setup and studies the size and power of the proposed permutation tests. Section 3 discusses implementation of the developed test. The finite-sample performance of the developed (smoothed or not) NPMLE-based permutation tests is investigated in Section 4. Section 5 applies the studied tests to a real scRNA-seq data containing single brain nuclei from autism subjects and healthy controls (Velmeshev et al., 2019) and discover significantly differentially expressed genes that cannot be detected using the benchmark DESeq2 method applied on pseudo-bulk data (Love et al., 2014). In Section 6, we

¹In addition to developing a more flexible non-parametric model, another route to boost the power of differential expression analysis is to de-noise the scRNA-seq data; see Zhang et al. (2021) for a proposal along that track.

justify the use of NPMLEs in the permutation tests outlined in Section 2 by providing minimax optimality results for the NPMLE for nonparametric mixture of Poissons. In the last section, Section 7 we provide outline of proofs. All the technical details of the proofs are relegated to a supplement.

Notation. For any two distributions P,Q on the real line, the Wasserstein-1 distance is defined to be $W_1(P,Q) := \sup_{\ell \in \text{Lip}_1} \int \ell(\mathsf{d}P - \mathsf{d}Q)$, where Lip_1 represents all 1-Lipschitz functions. For any distribution P on the nonnegative real line, we define its Poisson smoothed version as

$$h_Q(x) := \int_0^\infty e^{-\lambda} \frac{\lambda^x}{x!} \mathrm{d}Q(\lambda), \ x = 0, 1, 2, \dots$$

For any two constants a, b, we denote $a \lor b := \max\{a, b\}$ and $a \land b := \min\{a, b\}$.

2 Permutation tests

2.1 Setup

Throughout this section, it is assumed that the observations are heterogeneous count data $\{X_{ij}^{(k)}, i \in [N_{jk}], j \in [n_k], k \in [K]\}$ with $N_{jk} = N_{jk,n} \to \infty$ and $n_k = n_{k,n} \to \infty$ as $n := \sum n_k \to \infty$. In contrast, $K \geq 2$ is assumed to be a fixed integer. It is further assumed that the probability measures $Q_j^{(k)}$'s in (1.1) have a common support [0, B] for some B > 0 that is known a priori (cf. appendix Section B for a real implementation) and kept to be fixed in this section; later in Section 6 we will explore a more general setting where $B = B_n$ is allowed to increase with n.

To facilitate the approach to distinguishing differences among the K groups, in addition to the measurement model (1.1) and the expression model (1.2), a third-layer "population model" is introduced to encourage independent and identically distributed (i.i.d.) randomness among each n_k within-group expression models:

for each
$$k \in [K]$$
: $Q_1^{(k)}, \dots, Q_{n_k}^{(k)} \overset{i.i.d.}{\sim} Q_k$. (population model) (2.1)

Here Q_k is understood to be a probability measure over the Prohorov-metric topology of the space of probability measures that are defined on the Borel σ -field of [0, B]; details about constructing Prohorov-metric topology are referred to Pages 72-73 in Billingsley (1999). Following the discussions in Sarkar and Stephens (2021, Section "Modeling scRNA-seq data"), we do not specify Q_k except for assuming boundedness and well-definedness.

To wrap up, the model considered in this manuscript, summarizing the three layers ((1.1), (1.2), (2.1)), is:

$$\left\{X_{ij}^{(k)}, i \in [N_{jk}], j \in [n_k], k \in [K]\right\} \text{ are independently distributed with PMFs}$$

$$\int \left[\int_0^B e^{-\lambda r_{ij}^{(k)}} \frac{\{\lambda r_{ij}^{(k)}\}^x}{x!} dQ(\lambda)\right] dQ_k(Q), \quad x = 0, 1, 2, \dots$$
(2.2)

Under the above model, it is understood that Q_1, \ldots, Q_K and $K \geq 2$ are fixed, all of which won't change with n. Besides Q_1, \ldots, Q_K and accordingly the random measures $Q_j^{(k)}$'s, the observations $X_{ij}^{(k)}$'s also depend on the read depths $r_{ij}^{(k)} = r_{ij,n}^{(k)}$'s that are allowed to change with n. We are hence faced with a triangular array of possibly highly heterogeneous observations.

2.2 Tests

Under Model (2.2), we are interested in testing the following null hypothesis,

$$H_0: \mathcal{Q}_1 = \mathcal{Q}_2 = \dots = \mathcal{Q}_K, \tag{2.3}$$

and aim to detect any population-level difference between groups. Note that here, due to the incorporation of read depths $r_{ij}^{(k)}$'s, the measurements themselves even within each group are generally not identically distributed; thus, a naive empirical distribution function based test could be substantially biased.

The main interest of this paper is to explore how robust a Fisher-Pitman-type test can be when each unobserved subject-level random measure $Q_j^{(k)}$ is replaced by a plug-in-type estimate $\widetilde{Q}_j^{(k)}$ and its Poisson-smoothed version $h_{\widetilde{Q}_j^{(k)}}$ calculated from the measurements $X_{1j}^{(k)},\ldots,X_{N_{jk}j}^{(k)}$. To this end, let's regulate $\widetilde{Q}_j^{(k)}$ as follows.

Definition 2.1. For any $j \in [n_k]$ and any $k \in [K]$, an estimator $\widetilde{Q}_j^{(k)}$ of $Q_j^{(k)}$ is said to be subject-specific conditionally W_1 -consistent (shorthanded as "conditionally W_1 -consistent") if it is (i) a function of $X_{1j}^{(k)}, \ldots, X_{N_{ik}j}^{(k)}$; (ii) of support [0, B]; and (iii) satisfying

$$E\left\{W_1\left(\widetilde{Q}_j^{(k)}, Q_j^{(k)}\right) \mid Q_j^{(k)}\right\} \to 0 \text{ as } N_{jk} = N_{jk,n} \to \infty$$
 (2.4)

for almost all $Q_i^{(k)}$ with regard to the measure \mathcal{Q}_k .

We next consider the Poisson-smoothed mixing distribution estimator

$$h_{\widetilde{Q}_j^{(k)}} := \int_0^\infty e^{-\lambda} \frac{\lambda^x}{x!} \mathrm{d} \widetilde{Q}_j^{(k)}(\lambda)$$

based on any conditionally W_1 -consistent estimator $\widetilde{Q}_j^{(k)}$. It justifies the use of smoothed NPMLEs as an alternative to directly using the original ones; see also Proposition 3.1 in Lambert and Tierney (1984) for more results as read depths are all forced to be equal.

Theorem 2.1. Suppose $\widetilde{Q}_{i}^{(k)}$ is conditionally W_1 -consistent. Then

$$E\left\{W_1\left(h_{\widetilde{Q}_j^{(k)}}, h_{Q_j^{(k)}}\right) \mid Q_j^{(k)}\right\} \to 0 \text{ as } N_{jk} = N_{jk,n} \to \infty$$

for almost all $Q_j^{(k)}$ with regard to the measure \mathcal{Q}_k .

A particularly appealing candidate estimator of the mixing distribution is the following NPMLE $\widehat{Q}_i^{(k)}$ with read depth incorporated:

$$\widehat{Q}_{j}^{(k)} \in \underset{Q \text{ of support }[0,B]}{\operatorname{argmax}} \sum_{i \in [N_{jk}]} \log \int_{0}^{\infty} e^{-\lambda r_{ij}^{(k)}} \frac{\{\lambda r_{ij}^{(k)}\}^{X_{ij}^{(k)}}}{X_{ij}^{(k)}!} dQ(\lambda). \tag{2.5}$$

Note that here $\widehat{Q}_{j}^{(k)}$ may not be unique due to read depths, and if there are multiple choices, pick any one of them (cf. Remark 3.1). We shall discuss the calculation of $\widehat{Q}_{j}^{(k)}$ in Section 3. The next theorem shows that NPMLEs are conditionally W_1 -consistent under no further assumptions on the population measures Q_k 's except for the already imposed bounded support one.

Theorem 2.2 (Conditionally W_1 -consistency of NPMLEs). Assume $N_{jk} = N_{jk,n} \to \infty$ as $n \to \infty$, $r_{ij}^{(k)} = r_{ij,n}^{(k)} \in [\gamma_0, \gamma_1]$ are uniformly upper and lower bounded by two positive universal constants γ_0, γ_1 , and \mathcal{Q}_k 's have a common fixed support [0, B]. We then have the NPMLEs $\widehat{\mathcal{Q}}_j^{(k)}$'s are all conditionally W_1 -consistent.

Remark 2.1. In the literature, consistency of NPMLEs of mixing distributions under the classical i.i.d. mixture distribution setup (corresponding to the case with all read depths identical to each other) has been studied in depth. Notable results include Kiefer and Wolfowitz (1956), Simar (1976), Pfanzagl (1988); note also the survey by Chen (Chen, 2017). However, although arising naturally from single-cell genomics modeling, read-depth-incorporated nonparametric mixture distributions have not received much attention in mathematical statistics and, to our knowledge, Theorem 2.2 delivers the first consistency result for NPMLEs under this heterogeneous setting.

Based on any conditionally W_1 -consistent estimators $\{\widetilde{Q}_j^{(k)}\}$ of $\{Q_j^{(k)}\}$ and their Poisson-smoothed versions $h_{\widetilde{Q}_j^{(k)}}$'s, the proposed ANOVA-type (pseudo-F) test statistics are

$$\widetilde{F} := \frac{\frac{1}{n} \sum\limits_{k_1, k_2 \in [K]} \sum\limits_{j_1 \in [n_{k_1}], j_2 \in [n_{k_2}]} W_1 \Big(\widetilde{Q}_{j_1}^{(k_1)}, \widetilde{Q}_{j_2}^{(k_2)}\Big)^2 - \sum\limits_{k \in [K]} \frac{1}{n_k} \sum\limits_{j_1, j_2 \in [n_k]} W_1 \Big(\widetilde{Q}_{j_1}^{(k)}, \widetilde{Q}_{j_2}^{(k)}\Big)^2}{\sum\limits_{k \in [K]} \frac{1}{n_k} \sum\limits_{j_1, j_2 \in [n_k]} W_1 \Big(\widetilde{Q}_{j_1}^{(k)}, \widetilde{Q}_{j_2}^{(k)}\Big)^2}$$

and

$$\widetilde{F}_h := \frac{\frac{1}{n} \sum\limits_{k_1, k_2 \in [K]} \sum\limits_{j_1 \in [n_{k_1}], j_2 \in [n_{k_2}]} W_1 \Big(h_{\widetilde{Q}_{j_1}^{(k_1)}}, h_{\widetilde{Q}_{j_2}^{(k_2)}} \Big)^2 - \sum\limits_{k \in [K]} \frac{1}{n_k} \sum\limits_{j_1, j_2 \in [n_k]} W_1 \Big(h_{\widetilde{Q}_{j_1}^{(k)}}, h_{\widetilde{Q}_{j_2}^{(k)}} \Big)^2}{\sum\limits_{k \in [K]} \frac{1}{n_k} \sum\limits_{j_1, j_2 \in [n_k]} W_1 \Big(h_{\widetilde{Q}_{j_1}^{(k)}}, h_{\widetilde{Q}_{j_2}^{(k)}} \Big)^2}.$$

It is ready to check that these two test statistics both reduce to the original one-way ANOVA statistic if the examined space is the real space equipped with the Euclidean norm. The studied statistics then generalize the one-way ANOVA statistics to the W_1 -metric measure space with different inputs (mixing distribution smoothed or not); similar generalizations have been made in various other (non-)Euclidean spaces (Anderson, 2001; Mielke and Berry, 2007; Petersen and Müller, 2019).

We then move on to introduce the corresponding permuted ANOVA-type test statistics. To this end, for each permutation $\pi:[n]\to[n]$, let $\Pi^{j,k}=(\Pi^{j,k}_1,\Pi^{j,k}_2):=\pi^\uparrow(j,k)$ represent the original subject and population indices corresponding to "the j-th subject in the k-th group" after permutation π . The permuted test statistics are

$$\widetilde{F}^{\pi} := \frac{\frac{1}{n} \sum\limits_{k_{1}, k_{2} \in [K]} \sum\limits_{j_{1} \in [n_{k_{1}}], j_{2} \in [n_{k_{2}}]} W_{1} \Big(\widetilde{Q}_{j_{1}}^{(k_{1})}, \widetilde{Q}_{j_{2}}^{(k_{2})}\Big)^{2} - \sum\limits_{k \in [K]} \frac{1}{n_{k}} \sum\limits_{j_{1}, j_{2} \in [n_{k}]} W_{1} \Big(\widetilde{Q}_{\Pi_{1}^{j_{1}, k}}^{(\Pi_{2}^{j_{1}, k})}, \widetilde{Q}_{\Pi_{1}^{j_{2}, k}}^{(\Pi_{2}^{j_{2}, k})}\Big)^{2}}{\sum\limits_{k \in [K]} \frac{1}{n_{k}} \sum\limits_{j_{1}, j_{2} \in [n_{k}]} W_{1} \Big(\widetilde{Q}_{\Pi_{1}^{j_{1}, k}}^{(\Pi_{2}^{j_{1}, k})}, \widetilde{Q}_{\Pi_{1}^{j_{2}, k}}^{(\Pi_{2}^{j_{2}, k})}\Big)^{2}}$$

and

$$\widetilde{F}_h^\pi := \frac{\frac{1}{n} \sum\limits_{k_1, k_2 \in [K]} \sum\limits_{j_1 \in [n_{k_1}], j_2 \in [n_{k_2}]} W_1\Big(h_{\widetilde{Q}_{j_1}^{(k_1)}}, h_{\widetilde{Q}_{j_2}^{(k_2)}}\Big)^2 - \sum\limits_{k \in [K]} \frac{1}{n_k} \sum\limits_{j_1, j_2 \in [n_k]} W_1\Big(h_{\widetilde{Q}_{\Pi_1^{j_1, k}}^{(\Pi_2^{j_1, k})}}, h_{\widetilde{Q}_{\Pi_1^{j_2, k}}^{(\Pi_2^{j_2, k})}}\Big)^2}{\sum\limits_{k \in [K]} \frac{1}{n_k} \sum\limits_{j_1, j_2 \in [n_k]} W_1\Big(h_{\widetilde{Q}_{\Pi_1^{j_1, k}}^{(\Pi_2^{j_1, k})}}, h_{\widetilde{Q}_{\Pi_1^{j_2, k}}^{(\Pi_2^{j_2, k})}}\Big)^2}{\sum\limits_{k \in [K]} \frac{1}{n_k} \sum\limits_{j_1, j_2 \in [n_k]} W_1\Big(h_{\widetilde{Q}_{\Pi_1^{j_1, k}}^{(\Pi_2^{j_1, k})}}, h_{\widetilde{Q}_{\Pi_1^{j_2, k}}^{(\Pi_2^{j_2, k})}}\Big)^2}{\sum\limits_{k \in [K]} \frac{1}{n_k} \sum\limits_{j_1, j_2 \in [n_k]} W_1\Big(h_{\widetilde{Q}_{\Pi_1^{j_1, k}}^{(\Pi_2^{j_1, k})}}, h_{\widetilde{Q}_{\Pi_1^{j_2, k}}^{(\Pi_2^{j_2, k})}}\Big)^2}$$

The following are the Fisher-Pitman-type permutation tests with nominal level α :

$$\widetilde{T}_{\alpha} := \begin{cases} 1, & \text{if } P(\widetilde{F}^{\pi} < \widetilde{F} \mid \widetilde{Q}_{j}^{(k)}, s) \ge 1 - \alpha, \\ 0, & \text{otherwise,} \end{cases}$$

and

$$\widetilde{T}_{h,\alpha} := \begin{cases} 1, & \text{if } P(\widetilde{F}_h^{\pi} < \widetilde{F}_h \mid \widetilde{Q}_j^{(k)}, s) \ge 1 - \alpha, \\ 0, & \text{otherwise,} \end{cases}$$

where the probability here is only with respect to the random permutation π .

As the (Poisson smoothed-)NPMLEs are chosen, the corresponding tests \widetilde{T}_{α} and $\widetilde{T}_{h,\alpha}$ are specified as \widehat{T}_{α} and $\widehat{T}_{h,\alpha}$.

2.3 Theory

This subsection provides the necessary theoretical support on the presented tests \widetilde{F}^{π} and \widetilde{F}_{h}^{π} . Particular focus is on the asymptotic size and consistency against Robinson-type ANOVA alternatives (cf. Theorem 3 in Robinson (1973)). To minimize assumptions and for presentation clearness, we are focused on the following balanced design case:

Assumption 2.1. The design is balanced so that $n_k = n/K$ and $N_{jk} = N$ for $j \in [n_k]$, $k \in [K]$. In addition, it is assumed that the sets $\{r_{ij}^{(k)}, i \in [N]\}$ are invariant with respect to both j and k.

Remark 2.2. We note that Assumption 2.1 can be weakened in a straightforward manner to allow for $n_k/n \to 1/K$, N_{jk} 's asymptotically comparable, and the sets $\{r_{ij}^{(k)}, i \in [N_{jk}]\}$ all weakly converge to a same probability measure that does not depend on the particular choice of j and k (see Shi et al. (2020, Proposition 2.2) as well as Deb and Sen (2021) for a similar setup in the recent independence testing literature). We however do not pursue these tracks but rather leave them to the readers of interest to verify.

Our first result concerns with the sizes of proposed tests, is of a finite-sample nature, and is a direct consequence of a long line of literature on permutation-based tests.

Theorem 2.3 (Size validity). We have, for any finite N and n, as long as H_0 in (2.3) and Assumption 2.1 hold,

$$P(\widetilde{T}_{\alpha} = 1|H_0) \le \alpha$$
 and $P(\widetilde{T}_{h,\alpha} = 1|H_0) \le \alpha$.

In the following, we are focused on asymptotic results with the balanced design and let $N = N_n \to \infty$ as $n \to \infty$. The next theorem is the main result of this subsection.

Theorem 2.4 (Test consistency). Consider $\widetilde{Q}_j^{(k)}$'s to be conditionally W_1 -consistent estimators of $Q_j^{(k)}$'s. If Assumption 2.1 holds, then the following two statements are true.

(a) Under any fixed alternative regarding Q_1, \ldots, Q_K such that

$$H_1: \frac{1}{K} \sum_{k \in [K]} E\left\{W_1\left(Q_1^{(k)}, Q_2^{(k)}\right)^2\right\} < \sum_{k_1 \neq k_2 \in [K]} \frac{E\left\{W_1\left(Q_1^{(k_1)}, Q_1^{(k_2)}\right)^2\right\}}{K(K-1)},\tag{2.6}$$

we have $\lim_{n\to\infty} P(\widetilde{T}_{\alpha}=1|H_1)=1$ for each $\alpha\in(0,1)$.

(b) Under any fixed alternative regarding Q_1, \ldots, Q_K such that

$$H_{1,h}: \frac{1}{K} \sum_{k \in [K]} E\left\{W_1\left(h_{Q_1^{(k)}}, h_{Q_2^{(k)}}\right)^2\right\} < \sum_{k_1 \neq k_2 \in [K]} \frac{E\left\{W_1\left(h_{Q_1^{(k_1)}}, h_{Q_1^{(k_2)}}\right)^2\right\}}{K(K-1)}, \tag{2.7}$$

we have $\lim_{n\to\infty} P(\widetilde{T}_{h,\alpha}=1|H_{1,h})=1$ for each $\alpha\in(0,1)$.

Specific to (smoothed-)NPMLEs, the following theorem is a direct consequence of Theorems 2.2-2.4.

Corollary 2.1. Suppose Assumption 2.1 and all conditions in Theorem 2.2 hold. Then the following are true for any $\alpha \in (0,1)$.

(a) For any finite N and n, as long as H_0 in (2.3) holds, we have

$$P(\widehat{T}_{\alpha} = 1|H_0) \le \alpha$$
 and $P(\widehat{T}_{h,\alpha} = 1|H_0) \le \alpha$.

(b) Concerning any fixed alternative H_1 (or H_{1h}), we have

$$\lim_{n \to \infty} P(\widehat{T}_{\alpha} = 1 \mid H_1) = 1 \quad \text{and} \quad \lim_{n \to \infty} P(\widehat{T}_{h,\alpha} = 1 \mid H_{1,h}) = 1.$$

3 Algorithms

This section presents three algorithms to calculate (2.5),

- (1) the vertex direction method (VDM), cf. Fedorov (1972), Simar (1976), Wu (1978a), Wu (1978b), Böhning (1982), and Lindsay (1983a);
- (2) the vertex exchange method (VEM), cf. Böhning (1985) and Böhning (1986);
- (3) the intra simplex direction method (ISDM), cf. Lesperance and Kalbfleisch (1992).

To simplify the notation, in this section we remove j, k from the subscript and use $\{X_i, i \in [N]\}$ and $\{r_i, i \in [N]\}$ to denote the sample points and the corresponding read-depths. Moreover, we use \widehat{Q} to denote the NPMLE defined in (2.5) based on $\{X_i, i \in [N] \text{ and } \{r_i, i \in [N]\}$. For a discrete measure G on [0, B] with support points $\{\lambda_m, m \in [M]\}$, let $G(\lambda_m)$ stand for the mass G assigned at λ_m for each $m \in [M]$. We define

$$\Phi(G) := \frac{1}{N} \sum_{i \in [N]} \log \left(\sum_{m \in [M]} G(\lambda_m) e^{-\lambda_m r_i} (\lambda_m r_i)^{X_i} \right)$$

and its directional derivative from G to δ_{λ} as

$$\Phi'(G,\delta_{\lambda}) := \lim_{\epsilon \to 0^+} \epsilon^{-1} \Big\{ \Phi\{(1-\epsilon)G \oplus \epsilon \delta_{\lambda}\} - \Phi(G) \Big\} = \frac{1}{N} \sum_{i \in [N]} \frac{e^{-\lambda r_i} (\lambda r_i)^{X_i}}{\sum_{m \in [M]} G(\lambda_m) e^{-\lambda_m r_i} (\lambda_m r_i)^{X_i}} - 1.$$

Here δ_{λ} represents the unit measure at $\lambda \in [0, B]$. Lastly, for any two signed measures ν_1 and ν_2 on the real line, we denote $\nu_1 \oplus \nu_2$ as the sum of ν_1 and ν_2 , and $\nu_1 \oplus \nu_2$ as the sum of ν_1 and $-\nu_2$.

With these notation, we are now ready to present the VDM, VEM, and ISDM algorithms for calculating \hat{Q} .

The VDM Algorithm

- Step 0 (Initialization). Select a point $\lambda_1 \in (0, B]$. Let $G_1 = \delta_{\lambda_1}$ be the initial value. Set the loop index L = 1.
- Step 1 If $\max_{\lambda \in [0,B]} \Phi'(G_L, \delta_{\lambda}) = 0$, then stop and return G_L . Otherwise, find $\lambda_{\max} = \underset{\lambda \in [0,B]}{\operatorname{argmax}} \Phi'(G_L, \delta_{\lambda})$.

Step 2 Find
$$\alpha_{\max} = \operatorname{argmax}_{\alpha \in [0,1]} \Phi \Big\{ (1-\alpha) G_L \oplus \alpha \delta_{\lambda_{\max}} \Big\}.$$

Step 3 Set
$$G_{L+1} = (1 - \alpha)G_L \oplus \alpha_{\max}\delta_{\lambda_{\max}}$$
. Set $L = L + 1$ and go to Step 1.

The VEM Algorithm

- Step 0 (Initialization). Select a point $\lambda_1 \in (0, B]$. Let $G_1 = \delta_{\lambda_1}$ be the initial value. Set the loop index L = 1.
- Step 1 If $\max_{\lambda \in [0,B]} \Phi'(G_L, \delta_{\lambda}) = 0$, then stop and return G_L . Otherwise, find $\lambda_{\max} = \underset{\lambda \in [0,B]}{\operatorname{argmax}} \Phi'(G_L, \delta_{\lambda})$ and $\lambda_{\min} = \underset{\lambda \in \operatorname{supp}(G_L)}{\operatorname{argmin}} \Phi'(G_L, \delta_{\lambda})$, where $\operatorname{supp}(G_L)$ stands for the support of G_L .

Step 2 Find
$$\alpha_{\max} = \operatorname{argmax}_{\alpha \in [0,1]} \Phi \Big\{ G_L \oplus \Big(\alpha G_L(\lambda_{\min}) (\delta_{\lambda_{\max}} \ominus \delta_{\lambda_{\min}}) \Big) \Big\}.$$

Step 3 Set
$$G_{L+1} = G_L \oplus \left(\alpha_{\max} G_L(\lambda_{\min})(\delta_{\lambda_{\max}} \ominus \delta_{\lambda_{\min}})\right)$$
. Set $L = L + 1$ and go to Step 1.

The ISDM Algorithm

- Step 0 (Initialization). Select a point $\lambda_1 \in (0, B]$. Let $G_1 = \delta_{\lambda_1}$ be the initial value. Set the loop index L = 1.
- Step 1 If $\max_{\lambda \in [0,B]} \Phi'(G_L, \delta_{\lambda}) = 0$, then stop and return G_L . Otherwise, find all local maxima $\lambda_{\max,1}, \ldots, \lambda_{\max,\mathcal{N}}$ of $\lambda \mapsto \Phi'(G_L, \delta_{\lambda})$ on [0,B], where \mathcal{N} represents the number of local maxima.
- Step 2 Find $(\alpha_{\max,0},\ldots,\alpha_{\max,\mathcal{N}}) = \underset{\alpha_0,\ldots,\alpha_{\mathcal{N}}}{\operatorname{argmax}} \Phi \Big\{ (1-\alpha_0)G_L \oplus \alpha_1 \delta_{\lambda_{\max,1}} \oplus \cdots \oplus \alpha_{\mathcal{N}} \delta_{\lambda_{\max,\mathcal{N}}} \Big\}$ subject to $\alpha_0 \geq 0, \alpha_1 \geq 0, \cdots, \alpha_{\mathcal{N}} \geq 0$ and $\alpha_0 + \alpha_1 + \cdots + \alpha_{\mathcal{N}} = 1$.

Step 3 Set $G_{L+1} = (1 - \alpha_{\max,0})G_L \oplus \alpha_{\max,1}\delta_{\lambda_{\max,1}} \oplus \cdots \oplus \alpha_{\max,\mathcal{N}}\delta_{\lambda_{\max,\mathcal{N}}}$. Set L = L + 1 and go to Step 1.

The convergence of VDM, VEM, and ISDM is guaranteed by the following theorem.

Theorem 3.1. Assuming $r_i > 0$ for each $i \in [N]$. For each of VDM, VEM and ISDM, if it stops for some L, then we have $\Phi(G_L) = \Phi(\widehat{Q})$; otherwise, $\Phi(G_L) \to \Phi(\widehat{Q})$ as $L \to \infty$.

Remark 3.1. Unlike in the traditional setting where all read depths are identical, when heterogeneous read depths are incorporated, although $G \mapsto \Phi(G)$ is still a concave function, there is no theoretical guarantee about the uniqueness of \widehat{Q} 's that maximize the objective function and whether the maximizer is unique or not is still open. This issue of computational uniqueness shall be compared to the parallel result in Theorem 2.2, which provides theoretical guarantee for the consistency of an arbitrary maximizer of the objective function as the sample size increases to infinity.

4 Simulation studies

This section aims to show that the two NPMLE-based (smoothed or not) tests presented in Section 2 cannot dominate each other. Throughout the whole section, we fix K = 2 and consider the following three designs across with several cases of population models.

Designs.

- (A) Balanced designs with all read depths set to be 1, $n_1 = n_2 = 10$, and $N_{jk} = 50$, 100, and 500 for each j, k.
- (B) Balanced designs with read-depth effects with $n_1 = n_2 = 10$ and $N_{jk} = 50$, 100 and 500 for each j, k. In addition, in each round of the simulation, $\{r_{i1}^{(1)}, i \in [N_{11}]\}$ are i.i.d. generated from Uniform (0.5, 1.5) and then let $r_{ij}^{(k)} = r_{i1}^{(1)}$ for each j, k.
- (C) A particular unbalanced design motivated by the single-cell RNA-seq data in Section 5 ahead, with $n_1 = 10, n_2 = 13$ and N_{jk} be as in Table 1. For each round of the simulation, $\{r_{ij}^{(k)}, i \in [N_{jk}], j \in [n_k], k \in [K]\}$ are i.i.d. generated from Uniform (0.5, 1.5).

$N_{1,1}$	$N_{2,1}$	$N_{3,1}$	$N_{4,1}$	$N_{5,1}$	$N_{6,1}$	$N_{7,1}$	$N_{8,1}$	$N_{9,1}$	$N_{10,1}$	$N_{1,2}$	$N_{2,2}$
388	1142	162	391	215	278	284	193	542	106	202	759
$N_{3,2}$	$N_{4,2}$	$N_{5,2}$	$N_{6,2}$	$N_{7,2}$	$N_{8,2}$	$N_{9,2}$	$N_{10,2}$	$N_{11,2}$	$N_{12,2}$	$N_{13,2}$	
415	69	327	431	414	451	275	733	422	65	362	

Table 1: N_{jk} in the unbalanced design (Design (C))

We then move on to specify the population model (2.1) used in our simulation studies. Hereafter, let Gam(a, b; B) denote a truncated Gamma distribution with a shape parameter a > 0, a rate parameter b > 0, and with any realization larger than B shrunken to B. Let $\{\Delta_j^{(k)}, j \in [n_k], k \in [K]\}$ be i.i.d. generated from Uniform(-1,1).

Population models.

- 1. (a) $Q_j^{(k)} \sim \text{Gam}(14 + \Delta_j^{(k)}, 7/4; 50)$ for each $j \in [n_k], k \in [2]$. (b) $Q_j^{(k)} \sim \text{Gam}(14 + \Delta_j^{(k)}, 7; 50)$ for each $j \in [n_k], k \in [2]$. (c) $Q_j^{(k)} \sim \text{Gam}(6 + \Delta_j^{(k)}, 1; 50)$ for each $j \in [n_k], k \in [2]$.
- 2. (a) $Q_j^{(1)} \sim \operatorname{Gam}(14 + \Delta_j^{(1)}, 7/4; 50)$ for $j \in [n_1]$ and $Q_j^{(2)} \sim \operatorname{Gam}(6 + \Delta_j^{(2)}, 3/4; 50)$ for $j \in [n_2]$. (b) $Q_j^{(1)} \sim \operatorname{Gam}(14 + \Delta_j^{(1)}, 7/3; 50)$ for $j \in [n_1]$ and $Q_j^{(2)} \sim \operatorname{Gam}(6 + \Delta_j^{(2)}, 1; 50)$ for $j \in [n_2]$. (c) $Q_j^{(1)} \sim \operatorname{Gam}(14 + \Delta_j^{(1)}, 7/2; 50)$ for $j \in [n_1]$ and $Q_j^{(2)} \sim \operatorname{Gam}(6 + \Delta_j^{(2)}, 3/2; 50)$ for $j \in [n_2]$.
- 3. (a) $Q_j^{(1)} \sim \operatorname{Gam}(4 + \Delta_j^{(1)}, 1; 20)$ for $j \in [n_1]$ and $Q_j^{(2)} \sim \operatorname{Gam}(5 + \Delta_j^{(2)}, 1; 20)$ for $j \in [n_2]$. (b) $Q_j^{(1)} \sim \operatorname{Gam}(5 + \Delta_j^{(1)}, 1; 20)$ for $j \in [n_1]$ and $Q_j^{(2)} \sim \operatorname{Gam}(6 + \Delta_j^{(2)}, 1; 20)$ for $j \in [n_2]$. (c) $Q_j^{(1)} \sim \operatorname{Gam}(6 + \Delta_j^{(1)}, 1; 20)$ for $j \in [n_1]$ and $Q_j^{(2)} \sim \operatorname{Gam}(7 + \Delta_j^{(2)}, 1; 20)$ for $j \in [n_2]$.
- 4. (a) $Q_j^{(1)} \sim \operatorname{Gamma}(11 + \Delta_j^{(1)}, 1; 50)$ for $j \in [n_1]$ and $Q_j^{(2)} \sim \operatorname{Gamma}(12 + \Delta_j^{(2)}, 1; 50)$ for $j \in [n_2]$. (b) $Q_j^{(1)} \sim \operatorname{Gamma}(12 + \Delta_j^{(1)}, 1; 50)$ for $j \in [n_1]$ and $Q_j^{(2)} \sim \operatorname{Gamma}(13 + \Delta_j^{(2)}, 1; 50)$ for $j \in [n_2]$. (c) $Q_j^{(1)} \sim \operatorname{Gamma}(13 + \Delta_j^{(1)}, 1; 50)$ for $j \in [n_1]$ and $Q_j^{(2)} \sim \operatorname{Gamma}(14 + \Delta_j^{(2)}, 1; 50)$ for $j \in [n_2]$.

Our focus is on examining as well as comparing the empirical performance of the tests \widehat{T}_{α} and $\hat{T}_{h,\alpha}$ with NPMLE calculated using the oracle B. Both of them are based on an exact critical value approximated by 1,000 Monte Carlo simulations. The underlying nominal significance level is 0.05. For each setting, 1,000 rounds of simulations were performed. We use VEM to compute NPMLEs with a stop tolerance 0.01. Optimization in Step 1 and Step 2 in VEM is implemented by the default interior-point algorithm in Matlab; see the support page of function 'fmincon' for further details.

Table 2 shows the empirical sizes and powers (rejection frequencies) of tests \widehat{T}_{α} and $\widehat{T}_{h,\alpha}$. In short, the results confirm our earlier theoretical claims on the sizes and powers of T_{α} and $T_{h,\alpha}$ in the different models and balanced designs (Designs (A) and (B)). Moreover, even under the unbalanced design (Design (C)), T_{α} and $T_{h,\alpha}$ still perform well in terms of their empirical sizes and powers.

Some more detailed comparisons between T_{α} and $\hat{T}_{h,\alpha}$ are in line. The following observations depend on the "signal strengths" D and D_h , defined as follows:

$$D := E\{W_1(Q_1^{(1)}, Q_1^{(2)})^2\} - \left(E\{W_1(Q_1^{(1)}, Q_2^{(1)})^2\} + E\{W_1(Q_1^{(2)}, Q_2^{(2)})^2\}\right)/2$$
(4.1)

and

$$D_h := E\{W_1(h_{Q_1^{(1)}}, h_{Q_1^{(2)}})^2\} - \left(E\{W_1(h_{Q_1^{(1)}}, h_{Q_2^{(1)}})^2\} + E\{W_1(h_{Q_1^{(2)}}, h_{Q_2^{(2)}})^2\}\right)/2. \tag{4.2}$$

First, empirical results for Model 1 illustrates that under H_0 , empirical powers are close to the nominal level $\alpha = 0.05$, confirming the size validity of \widehat{T}_{α} and $\widehat{T}_{h,\alpha}$. In addition, even under the unbalanced design (Design (C)), empirical powers are stable and close to the nominal level $\alpha = 0.05$, indicating the robustness of the studied tests.

Second, we compare the empirical powers using Models 2, 3, and 4. In Model 2, D is significantly larger than D_h and the corresponding empirical powers of \widehat{T}_{α} are all larger than these of $\widehat{T}_{h,\alpha}$ in all three considered designs (Designs (A), (B), and (C)). This phenomenon is not surprising to us as the difference between variation between groups and variation within groups in mixing distributions is much larger than that in mixture distributions. Therefore, \widehat{T}_{α} is more powerful than $\widehat{T}_{h,\alpha}$.

In Model 3, D is approximately equal to D_h and the empirical power of \widehat{T}_{α} is smaller than the empirical power of $T_{h,\alpha}$ when N is small (e.g., 50 and 100). However, the empirical powers of T_{α} and

Table 2: Empirical sizes and powers of \widehat{T}_{α} and $\widehat{T}_{h,\alpha}$; here D and D_h are defined in (4.1) and (4.2)

Model	1(a)	1(b)	1(c)	2(a)	2(b)	2(c)	3(a)	3(b)	3(c)	4(a)	4(b)	4(c)
D	0	0	0	0.59	0.32	0.15	0.99	0.99	0.99	0.99	0.99	0.99
D_h	0	0	0	0.22	0.10	0.03	0.99	0.99	0.99	0.99	0.99	0.99
N		Empirical sizes/powers for \widehat{T}_{α} under Design (A)										
50	0.054	0.050	0.045	0.644	0.595	0.356	0.811	0.772	0.698	0.538	0.501	0.502
100	0.043	0.055	0.053	0.901	0.835	0.583	0.870	0.872	0.843	0.723	0.680	0.668
500	0.049	0.049	0.060	0.996	0.999	0.965	0.952	0.958	0.941	0.850	0.831	0.829
N	Empirical sizes/powers for $\widehat{T}_{h,\alpha}$ under Design (A)											
50	0.054	0.045	0.049	0.284	0.210	0.111	0.833	0.816	0.767	0.650	0.635	0.624
100	0.038	0.063	0.049	0.371	0.264	0.138	0.896	0.892	0.882	0.797	0.788	0.771
500	0.042	0.047	0.055	0.492	0.309	0.186	0.951	0.961	0.947	0.944	0.924	0.921
N	Empirical sizes/powers for \widehat{T}_{α} under Design (B)											
50	0.044	0.048	0.058	0.644	0.508	0.338	0.796	0.763	0.729	0.559	0.522	0.520
100	0.053	0.050	0.062	0.863	0.779	0.518	0.878	0.862	0.846	0.714	0.735	0.679
500	0.036	0.052	0.054	1.000	0.998	0.972	0.958	0.952	0.939	0.922	0.920	0.913
N	Empirical sizes/powers for $\widehat{T}_{h,\alpha}$ under Design (B)											
50	0.044	0.050	0.054	0.262	0.193	0.100	0.821	0.806	0.772	0.632	0.619	0.602
100	0.058	0.041	0.053	0.350	0.276	0.132	0.885	0.877	0.858	0.772	0.788	0.759
500	0.036	0.045	0.057	0.501	0.414	0.187	0.956	0.950	0.943	0.932	0.928	0.924
N	Empirical sizes/powers for \widehat{T}_{α} under Design (C)											
Table 1	0.048	0.050	0.051	0.994	0.988	0.900	0.962	0.940	0.951	0.910	0.904	0.907
NT	^											
N	0.047	0.051									0.000	0.000
Table 1	0.047	0.051	0.052	0.452	0.346	0.173	0.966	0.947	0.952	0.929	0.920	0.922

 $\widehat{T}_{h,\alpha}$ are close when N is large. Similar observation applies to Model 4, where D is also approximately equal to D_h . However, compared to Model 3, the mixing distributions in Model 4 have larger B and thus the empirical powers of $\widehat{T}_{h,\alpha}$ are higher than the empirical powers of \widehat{T}_{α} even for N=500, especially under Design (A). Some pilot studies to explain this phenomenon will be put in Section 6, where we analyze the finite-sample behavior of the NPMLE under an exploratory simplified setting where all read depths are fixed to be 1. There, the rate of convergence of NPMLE, at the worst case, is showed to be $O(\log\log N/\log N)$; in contrast, Lambert and Tierney (1984, Lemma 4.1 and Theorem 4.1) showed that the Poisson-smoothed NPMLE attains a near-root-n rate of convergence to the mixture distribution.

5 Applications to single-cell genomics

This section applies the studied permutation tests to a scRNA-seq data. There has been a large literature studying fitting RNA-seq data using Poisson mixtures including, e.g., over-dispersed Poisson model (Robinson et al., 2010), Poisson-Gamma model (Love et al., 2014; Huang et al., 2018), Poisson-Beta model (Vu et al., 2016), Poisson-log normal model (Silva et al., 2019), Poisson mixture model with K-clusters (Rau et al., 2015), finite Poisson mixture models (Wu et al., 2013), zero-inflated mixture Poisson linear models (Liu et al., 2019), Poisson mixture models with unimodal mixing distributions (Lu, 2018). Compared to parametric Poisson mixture models, nonparametric Poisson mixture models haven't received much attention; some notable exceptions include Bi and Davuluri (2013), Dadaneh et al. (2018), Sarkar and Stephens (2021), the latter of which was closely followed by us.

5.1 Data set description

The scRNA-seq data used in this paper is obtained from Velmeshev et al. (2019), which focused on autism spectrum disorder (ASD) and recorded gene expression of 23 subjects (13 ASD v.s. 10 control) and 18,041 genes for each subject from 17 different cell types and 2 different brain regions. Here we focus on the brain region prefrontal cortex, which is more relevant to autism disease etiology. Moreover, each subject has 7 covariates including age, sex, diagnosis, capbatch, post-mortem interval (PMI), and RNA integrity number (RIN).

We focus on a pre-selected subset including 100 genes (names of the genes put in Table 3) that were documented to be related to body height; for relation between ASD and body height, see, e.g., Fukumoto et al. (2011) and Chawarska et al. (2011). In addition to permutation testing with either estimated mixing distributions or mixture distributions, we also consider DESeq2 (Love et al., 2014) as a benchmark. In implementing the two considered permutation tests, we adopt a common strategy to incorporate four covariates age, sex, seqbatch, and RIN. The other two covariates PMI and capbatch are not significantly associated with gene expression given the other covariates, since their p-value distributions across all genes are uniform. The corresponding tests were denoted as \hat{T}_Z (with the original NPMLE) and $\hat{T}_{h,Z}$ (with the Poisson-smoothed NPMLE). Details of the implementation were put in appendix Section B.

5.2 Implementation results

Using \widehat{T}_Z , 9 genes are significant under the threshold of false discovery rate (FDR) 0.05 after multiple testing correction by the Benjamini-Hochberg procedure. Replacing \widehat{T}_Z by $\widehat{T}_{h,Z}$, 8 genes are significant under the same threshold of FDR and 7 genes are coincident with significant genes found by \widehat{T}_Z . This shows some consistency between \widehat{T}_Z and $\widehat{T}_{h,Z}$.

Furthermore, by DESeq2 there are 7 significant genes under the same threshold of FDR and all of them are coincident with significant genes found by \widehat{T}_Z . In other words, among significant genes found by \widehat{T}_Z , 78% significant genes are coincident with genes found by DESeq2 and 22% are new which means \widehat{T}_Z could enrich the set of significant genes found by the standard method DESeq2.

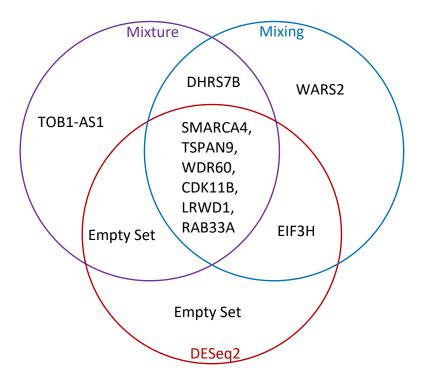


Figure 1: Significant genes selected using Mixing (\widehat{T}_Z) , Mixture $(\widehat{T}_{h,Z})$, and DESeq2 methods.

Similarly, 6 genes are coincident with significant genes found by $\widehat{T}_{h,Z}$. In other words, among significant genes found by $\widehat{T}_{h,Z}$, 75% significant genes are coincident with genes found by DESeq2 and 25% are new which means $\widehat{T}_{h,Z}$ could enrich the set of significant genes found by the standard method DESeq2. In one word, both \widehat{T}_Z and $\widehat{T}_{h,Z}$ could enrich the set of significant genes found by DESeq2. Further details are summarized in Figure 1.

Our results can also be justified by functions of significant genes. For example, fasting blood glucose measurement is not only one of functions of gene DHRS7B, but also related to ASD (Hoirisch-Clapauch and Nardi, 2019). More such results are summarized in Table 4.

6 Minimax optimality of the Poisson NPMLEs

This section provides additional theoretical support for the use of NPMLEs in forming up the tests \widehat{T}_{α} and $\widehat{T}_{h,\alpha}$ in Section 2. To this end, due to the technical challenges, focus is restricted to a simplified setting of (2.2), where the observations $\{X_i, i \in [N]\}$ independently follow a distribution of PMF

$$h_Q(x) = \int_0^B e^{-\lambda} \frac{\lambda^x}{x!} dQ(\lambda), \quad x = 0, 1, 2, \dots,$$
 (6.1)

where Q is a deterministic measure supported on [0, B] that cannot be characterized by a simple parametric model. This is exactly the classic nonparametric Poisson mixture setup, and we study

Table 3: All genes used in Section 5

DST	CHSY3	TSC2	EHD4	HERC1	KIF16B	DLGAP1	PIK3CG
ELL	ODF2L	FBXL5	LNX1	ERGIC3	CBFA2T2	FAM20A	STAT2
DAP	SSH2	WDR60	SAXO1	FOXP2	SAMD4A	TSPAN9	ARAP3
GHR	KCNK9	RGL1	SOCS5	ZNF76	ADAMTS2	DHRS7B	PNMA8C
KIZ	SHPRH	RBMS3	MFSD2B	NR4A3	CCDC171	RAB33A	WDR70
IL16	MTMR3	CDK10	ZNF628	CAPZB	ATXN7L3	PSKH1	FGFRL1
BST2	UMAD1	CPED1	ESYT2	LRRC43	SMARCA4	MYO18A	IL17RD
LHX2	FBP2	ZC3H13	SRRM2	NOTCH1	HSD17B3	SBNO1	EIF3H
RLF	LAYN	SUSD5	DOT1L	WARS2	RPS4XP13	PHF11	CDK11B
DAZL	CYFIP2	ST7L	CWC27	C9orf152	TOB1-AS1	HIF1AN	KLHL28
BCL9	LRWD1	LMO7	PTENP1	CEP112	LINC01572	PPP4R2	UBE2Z
NRK	GCLC	PPM1H	ITGA9	HIP1R	PPP1R16A	POLR3E	TANC2
ANKDD1A		ZNF710-AS1		ZRANB2-AS2		DNAJC27-AS1	

Table 4: Significant genes on ASD with some literature support. The first column includes names of genes, the second column includes functions potentially related to ASD, and the third column includes literatures supports

gene name	related functions	literatures
DHRS7B	fasting blood glucose measurement	Hoirisch-Clapauch and Nardi (2019)
WDR60	abnormality of refraction	Ezegwui et al. (2014)
EIF3H	reaction time measurement	Baisch et al. (2017)
LRWD1	insomnia measurement	Hohn et al. (2019)
RAB33A	bipolar disorder	Joshi et al. (2012)
TSPAN9	creatinine measurement	Cameron et al. (2017)
WARS2, CDK11B	heel bone mineral density	Calarge and Schlechte (2017)
SMARC4, TOB1-AS1	cholesterol measurement	Benachenhou et al. (2019)

the nonasymptotic behavior of the following NPMLE

$$\widehat{Q} = \underset{Q \text{ of support } [0,B]}{\operatorname{argmax}} \sum_{i \in [N]} \log h_Q(X_i). \tag{6.2}$$

Note that, the above NPMLE is the simplified version of (2.5) with all read depths there forced to be one.

There has been an enormous literature studying the NPMLE (6.2) under the nonparametric Poisson mixture model (6.1). Earlier results on the existence, discreteness (of the NPMLE support), and computation include, among many others, Simar (1976), Laird (1978), Jewell (1982), Lindsay (1983a), Lindsay (1983b), and Lindsay and Roeder (1993); see also Lindsay (1995) for a survey. Consistency of NPMLEs were established in, among many others, Kiefer and Wolfowitz (1956), Simar (1976), and Pfanzagl (1988); see also Chen (2017) for a survey.

Beyond these important results, there has been another track of substantial research that is focused on establishing the minimax rate in estimating the mixing distribution (mostly on the density function) of nonparametric Poisson mixtures. Notable results there include, e.g., Zhang (1995), Loh and Zhang (1996), van de Geer (1996), Hengartner (1997), van de Geer (2003), Roueff and Rydén (2005), and Rebafka and Roueff (2015). However, to our knowledge, a study on the minimax optimality and the corresponding convergence rates for NPMLEs under a fully nonparametric Poisson mixture model is still absent from the literature.

We would love to highlight again that, due to the nature of nonasymptotic analysis, all the parameters in the model, including B, are allowed to change with N. This is a strict generalization of the "asymptotic" setting in Section 2, where, due to the additional hardness of handling the read depth as well as for simplifying notation and assumptions, we do not intend to establish similar nonasymptotic results.

Our first theorem concerns with the NPMLE's rate of convergence.

Theorem 6.1 (Upper bound of NPMLEs).

(a) Suppose there exists a universal constant $c_0 > 0$ such that $B \le c_0 \log N$. Then there exists a positive constant $C = C(c_0)$ such that for all sufficiently large N (> $N_0(c_0)$) we have

$$\sup_{Q \text{ of support } [0,B]} E\Big\{W_1(\widehat{Q},Q)\Big\} \leq C \frac{B}{\log N} \log \left(\frac{\log N}{B} \vee e\right).$$

(b) Suppose there exist universal strictly positive constants c_0, C_0 and $\epsilon_0 \in (0, 1/3)$ such that $B \in [c_0 \log N, C_0 N^{1/3 - \epsilon_0}]$. Then there exists a strictly positive constant $C = C(\epsilon_0, c_0)$ such that for all sufficiently large N (> $N_0(c_0, C_0, \epsilon_0)$) we have

$$\sup_{Q \text{ of support } [0,B]} E\Big\{W_1(\widehat{Q},Q)\Big\} \le C\sqrt{\frac{B}{\log N}}.$$

Our second theorem concerns with minimax lower bounds in estimating mixing distributions in model (6.1). Combined with Theorem 6.1, it confirms the NPMLE's minimax optimality.

Theorem 6.2 (Minimax lower bound of mixing distribution estimation).

(a) Supposing there exists $c_0 > 0$ such that $B \le c_0 \log N$, it follows that for any $N \ge 3$,

$$\inf_{\widetilde{Q}} \sup_{Q} E\{W_1(\widetilde{Q},Q)\} \ge \frac{B}{24e \log N} \log \Big(\frac{16c_0 \log N}{B}\Big).$$

(b) Supposing there exists $c_0 > 0$ such that $B \ge c_0 \log N$, it follows that for any $N \ge 1$,

$$\inf_{\widetilde{Q}} \sup_{Q} E\{W_1(\widetilde{Q}, Q)\} \ge \frac{3}{40e^4} \sqrt{\frac{B}{c_0 \log N}}.$$

In the above, the infimum and supremum are understood to be taken over all estimators and all distributions of support [0, B]

Remark 6.1. Under fully nonparametric binomial mixture models, minimax optimal convergence rates for NPMLEs of mixing distributions were obtained by Vinayak et al. (2019, Section 3) in terms of the W_1 distance. Under fully nonparametric binomial and Gaussian mixture models, Tian et al. (2017, Theorem 1) and Wu and Yang (2020a, Page 1985) obtained optimal convergence rates for moment-based estimators in terms of W_1 distance; see also Polyanskiy and Wu (2020, Remark 2). Nguyen et al. (2013, Theorems 1 and 2) upper bounded the Wasserstein distance between mixing distributions by the divergence between the corresponding mixture distributions under general mixture models, with normal mixture models as an example in Example 2. However, their results cannot be applied here since Theorem 1 restricts the mixing distribution being discrete and Theorem 2 is only for convolution mixture models.

7 Proofs

7.1 Proofs of theorems in Section 2

Proof of Theorem 2.1. To simplify notations, we temporarily drop the subject index j and the group index k in this proof. A restatement of this theorem is then as follows:

suppose there exists an estimator $\widetilde{Q} = \widetilde{Q}_N$ on [0,B] such that $E\{W_1(\widetilde{Q},Q) \mid Q\} \to 0$ as $N = N_n \to \infty$ for almost all Q with regard to the measure Q. Then we have $E\{W_1(h_{\widetilde{Q}},h_Q) \mid Q\} \to 0$ as $N = N_n \to \infty$ for almost all Q with regard to the measure Q.

This proof consists of three steps. In the first step, we assume both Q and \widetilde{Q} 's are ordinary distributions with no randomness and prove that $W_1(\widetilde{Q},Q) \to 0$ implies $W_1(h_{\widetilde{Q}},h_Q) \to 0$. In the second step, we temporarily forget the third-layer "population model" (2.1) and prove that $E\{W_1(\widetilde{Q},Q)\}\to 0$ implies $E\{W_1(h_{\widetilde{Q}},h_Q)\}\to 0$ where the expectation is with respect to randomness from the "measurement model" (1.1) and "expression model" (1.2). In the third step, the third-layer "population model" (2.1) gets involved and we complete this proof.

Step 1. Suppose $\{\widetilde{Q}\}$ is a sequence of ordinary distributions with no randomness. To prove that $W_1(\widetilde{Q},Q) \to 0$ implies $W_1(h_{\widetilde{Q}},h_Q) \to 0$, note that $W_1(\widetilde{Q},Q) \to 0$ is equivalent to $\widetilde{Q} \stackrel{d}{\to} Q$ supplemented with $E\{|\widetilde{Q}|\} \to E\{|Q|\}$ (Panaretos and Zemel, 2019, Section 2.3). Moreover, it follows from Skorokhod's representation theorem that we can assume $\widetilde{Q} \stackrel{a.s.}{\to} Q$. To prove $W_1(h_{\widetilde{Q}},h_Q) \to 0$,

it suffices to prove that $h_{\widetilde{Q}} \stackrel{d}{\to} h_Q$ and $E\{h_{\widetilde{Q}}\} \to E\{h_Q\}$, where the second part follows immediately from $E\{h_{\widetilde{Q}}\} = E\{\widetilde{Q}\}$ and $E\{h_Q\} = E\{Q\}$. For the first part, it follows from $e^{-\lambda}\lambda^x \leq (x/e)^x$ for all $\lambda \in \mathbb{R}^+$ and the dominated convergence theorem that

$$h_{\widetilde{Q}}(x) = \int_0^B e^{-\lambda} \frac{\lambda^x}{x!} d\widetilde{Q}(\lambda) \to \int_0^B e^{-\lambda} \frac{\lambda^x}{x!} dQ(\lambda) = h_Q(x).$$

Step 2. Now suppose $\{\widetilde{Q}\}$ is a sequence of estimators for Q with randomness from the "measurement model" (1.1) and "expression model" (1.2). Then it can be proved that $W_1(\widetilde{Q},Q) \stackrel{p}{\to} 0$ implies $W_1(h_{\widetilde{Q}},h_Q) \stackrel{p}{\to} 0$ based on the result in **Step 1** and the fact that a sequence converging in probability is equivalent to that its every subsequence has a further subsequence that converges almost surely. To prove $E\{W_1(\widetilde{Q},Q)\} \to 0$ implies $E\{W_1(h_{\widetilde{Q}},h_Q)\} \to 0$, it suffices to verify that $E\{W_1(h_{\widetilde{Q}},h_Q)^2\}$ is bounded which follows immediately from Proposition 7.1, or specifically,

$$W_1(h_{\widetilde{Q}}, h_Q) \le E\{h_{\widetilde{Q}}\} + E\{h_Q\} = E\{\widetilde{Q}\} + E\{Q\} \le 2B.$$

Step 3. Suppose \mathbb{Q}_B is a set consisting of all distributions on [0, B]. For any $Q_0 \in \mathbb{Q}_B$ with $E\{W_1(\widehat{Q}, Q) \mid Q = Q_0\} \to 0$, it follows from **Step 2** that

$$E\{W_1(h_{\widetilde{Q}},h_Q) \mid Q=Q_0\} = E\{W_1(h_{\widetilde{Q}},h_{Q_0}) \mid Q=Q_0\} = E\{W_1(h_{\widetilde{Q}},h_{Q_0})\} \to 0,$$

where the expectation in the last term $E\{W_1(h_{\widetilde{Q}}, h_{Q_0})\}$ is with respect to the randomness from the "measurement model" (1.1) and "expression model" (1.2) only. Then we can complete this proof by noting that $P(Q \in \mathbb{Q}_B) = 1$.

Proof of Theorem 2.2. To simplify notations, we temporarily drop the subject index j and the group index k in this proof. A restatement of this theorem is accordingly as follows:

assume $N = N_n \to \infty$ as $n \to \infty$, $r_i = r_{i,n} \in [\gamma_0, \gamma_1]$ are uniformly upper and lower bounded by two positive universal constants γ_0, γ_1 , and Q is supported on [0, B]. We then have $E\{W_1(\widehat{Q}, Q) \mid Q\} \to 0$ as $n \to \infty$ for almost all Q with regard to the measure Q.

This proof consists of two steps. In the first step, we temporarily drop further the third-layer "population model" (2.1) and prove that for each fixed distribution Q supported on [0, B] we have $E\{W_1(\widehat{Q}, Q)\} \to 0$ as $n \to \infty$, where the expectation is with respect to randomness from the "measurement model" (1.1) and "expression model" (1.2). In the second step, the third-layer "population model" (2.1) gets involved and we complete the proof of the conditional W_1 -consistency of \widehat{Q} .

Step 1. The first step consists of three substeps. In the first substep, we prove that the set containing all distributions which are at least $\delta > 0$ far from Q can be covered by finite open balls in W_1 distance. In the second substep, with the aid of finite balls, we prove that, with probability converging to 1, no distributions that are at least δ far away from Q can maximize the likelihood function and hence the W_1 distance between \widehat{Q} and Q is less than δ . Then the W_1 consistency of \widehat{Q} follows immediately from picking a arbitrarily small δ .

Step 1(a). Let \mathbb{Q}_B be a metric space consisting of all distributions supported on [0, B] with the W_1 distance. For any $\delta > 0$, define

$$\mathcal{B}_{\delta}(Q) := \left\{ Q' \in \mathbb{Q}_B : W_1(Q', Q) < \delta \right\}$$

and its complement is denoted by $\mathcal{B}_{\delta}^{c}(Q)$.

In the sequel, fix ϵ to be a small positive number. Suppose Q_1, Q_2 are two distributions on [0, B] and F_{Q_1}, F_{Q_2} are their distribution functions. It then follows from

$$e^{-B} \int_0^B |F_{Q_1} - F_{Q_2}| \le \int_0^B |F_{Q_1}(\lambda) - F_{Q_2}(\lambda)| e^{-\lambda} \mathrm{d}\lambda \le \int_0^B |F_{Q_1} - F_{Q_2}| e^{-B} \int_0^B |F_{Q_1}$$

that Kiefer-Wolfowitz distance Chen (2017, page 51) and Wasserstein-1 distance induce the same topology on \mathbb{Q}_B . Hence it follows from Chen (2017, page 54) that that there exists a finite number of distributions $Q_j \in \mathbb{Q}_B$, $j \in [J]$, such that

$$\mathcal{B}^{c}_{\delta}(Q) \subset \bigcup_{j \in [J]} \mathcal{B}_{\epsilon}(Q_{j}).$$

Without loss of generality, it is assumed that Q_j is neither a deterministic distribution at 0 (in other words, degenerate distribution at 0) nor Q for each $j \in [J]$.

Step 1(b). Let $Y_{j,\epsilon}(r) := \log \left\{ 1 + u \left(h_{r,Q}(H_{r,Q}^{-1}(U)) / h_{r,\mathcal{B}_{\epsilon}(Q_j)}(H_{r,Q}^{-1}(U)) - 1 \right) \right\}$, where $r \in [\gamma_0, \gamma_1]$, $u \in (0,1)$, $h_{r,Q}(x) := \int_0^B e^{-r\lambda} \frac{(r\lambda)^x}{x!} dQ(\lambda)$, $h_{r,\mathcal{B}_{\epsilon}(Q_j)}(x) := \sup_{Q' \in \mathcal{B}_{\epsilon}(Q_j)} h_{r,Q'}(x)$, U is a uniform random variable on [0,1], and $H_{r,Q}^{-1}(\cdot)$ is a function such that $H_{r,Q}^{-1}(U) \sim h_{r,Q}$.

(i) We first prove that there exist constants $\epsilon_j > 0$ and $c_j > 0$ such that for all $\epsilon \leq \epsilon_j$ and $r \in [\gamma_0, \gamma_1]$ we have $E\{Y_{j,\epsilon}(r)\} \geq c_j > 0$.

Note that $Y_{j,\epsilon}(r) \ge \log(1-u)$ and $\lim_{\epsilon \to 0^+} Y_{j,\epsilon}(r) = Y_{j,0^+}(r)$ almost surely, where

$$Y_{j,0^+}(r) := \log \left\{ 1 + u \left(h_{r,Q}(H_{r,Q}^{-1}(U)) / h_{r,Q_j}(H_{r,Q}^{-1}(U)) - 1 \right) \right\}.$$

Since $Y_{j,\epsilon}(r)$ is monotonically decreasing with respect to ϵ , it follows from the monotone convergence theorem that $\lim_{\epsilon \to 0^+} E\{Y_{j,\epsilon}(r)\} = E\{Y_{j,0^+}(r)\}$ for each $r \in [\gamma_0, \gamma_1]$. Moreover, it follows from Lemma 2.5 in Chen (2017) that $E\{Y_{j,0^+}(r)\} > 0$ for each $r \in [\gamma_0, \gamma_1]$. Since $E\{Y_{j,0^+}(r)\}$ is a continuous function with respect to r and $r \in [\gamma_0, \gamma_1]$, there exists a positive constant c_j such that $E\{Y_{j,0^+}(r)\} \ge 2c_j$ for all $r \in [\gamma_0, \gamma_1]$. Furthermore, since $E\{Y_{j,\epsilon}(r)\}$ is a monotonically decreasing function with respect to ϵ , then it follows from Dini's theorem that $E\{Y_{j,\epsilon}(r)\}$ uniformly converges to $E\{Y_{j,0^+}(r)\}$ as $\epsilon \to 0^+$ on $r \in [\gamma_0, \gamma_1]$ and hence there exists a ϵ_j which doesn't depend on r such that for all $\epsilon \le \epsilon_j$ and $r \in [\gamma_0, \gamma_1]$ we have $|E\{Y_{j,\epsilon}(r)\} - E\{Y_{j,0^+}(r)\}| \le c_j$. Hence $E\{Y_{j,\epsilon}(r)\} \ge c_j > 0$ for all $\epsilon \le \epsilon_j$ and $r \in [\gamma_0, \gamma_1]$. Replacing r by $r_{i,n}$ for all $\epsilon \le \epsilon_j$ we have

$$E\{Y_{j,\epsilon}(r_{i,n})\} \ge c_j > 0 \text{ for all } i \in [N_n].$$

In the following arguments, set $\epsilon = \min_{j \in [J]} \{ \epsilon_j \}$ and let $\mathcal{B}_j := \mathcal{B}_{\epsilon}(Q_j)$ for simplicity.

(ii) We then prove that there exists a constant C_j such that $\operatorname{Var}\{Y_{j,\epsilon}(r)\} \leq C_j < \infty$ for all $r \in [\gamma_0, \gamma_1]$.

Since $h_{r,\mathcal{B}_j}(x) \ge h_{r,Q_j}(x)$ and $\log\{1 + u(h_{r,Q}(x)/h_{r,\mathcal{B}_j}(x) - 1)\} \ge \log(1 - u)$, we have $E\{Y_{j,\epsilon}^2(r)\} < 0$

 ∞ or equivalently

$$E\{\left(\log\{1 + u(h_{r,Q}(X_r)/h_{r,\mathcal{B}_i}(X_r) - 1)\}\right)^2\} < \infty$$

where $X_r := H_{r,Q}^{-1}(U) \sim h_{r,Q}$, as long as $E\{(h_{r,Q}(X_r)/h_{r,Q_r}(X_r)-1)^2\} < \infty$, or simply,

$$E\{(h_{r,Q}(X_r)/h_{r,Q_j}(X_r))^2\}<\infty.$$

To prove it, note that Q_i is not a deterministic distribution at 0 and hence there exist $\lambda_i \in (0, B]$ such that $F_{Q_i}(\lambda_j) < 1$. Then we have

$$h_{r,Q}(x) \le e^{-B\gamma_1} \frac{(B\gamma_1)^x}{x!}$$
 and $h_{r,Q_j}(x) \ge (1 - F_{Q_j}(\lambda_j)) e^{-\gamma_0\lambda_j} \frac{(\gamma_0\lambda_j)^x}{x!}$

for sufficiently large x, and hence

$$\frac{h_{r,Q}(x)}{h_{r,Q_j}(x)} \le \frac{e^{\gamma_0 \lambda_j - B\gamma_1}}{\left(1 - F_{Q_j}(\lambda_j)\right)} \left(\frac{B\gamma_1}{\gamma_0 \lambda_j}\right)^x.$$

Then $E\{(h_{r,Q}(X_r)/h_{r,Q_j}(X_r))^2\}$ < ∞ follows immediately from the existence of the moment generating function of Poisson distribution. Since $E\{Y_{i,\epsilon}^2(r)\}$ is a continuous function with respect to r and $r \in [\gamma_0, \gamma_1]$, then there exists a uniform constant C_j such that

$$E\{Y_{j,\epsilon}^2(r)\} \leq C_j$$

for all $r \in [\gamma_0, \gamma_1]$. Replacing r by $r_{i,n}$ it follows that $E\{Y_{j,\epsilon}^2(r_{i,n})\} \leq C_j$ for all $i \in [N_n]$. (iii) Suppose $X_{i,n}, i \in [N_n]$ is a sequence of independent random variables with $X_{i,n} \sim h_{r_{i,n},Q}$. Define $Z_{ij,n} := \log \left\{ 1 + u \left(h_{r_{i,n},Q}(X_{i,n}) / h_{r_{i,n},\mathcal{B}_{\epsilon}(Q_j)}(X_{i,n}) - 1 \right) \right\}$. Note that $Z_{ij,n} \stackrel{d}{=} Y_{j,\epsilon}(r_{i,n})$. Built on (i) and (ii), we have $E\{Z_{ij,n}\} \ge c_j > 0$ and $\operatorname{Var}\{Z_{ij,n}\} \le C_j < \infty$ for $i \in [N_n]$ and $j \in [J]$. Therefore.

$$\operatorname{Var}\left\{\sum_{i\in[N_n]} Z_{ij,n}\right\} \le N_n C_j$$

and hence $\operatorname{Var}\left\{\sum_{i\in[N]} Z_{ij,n}\right\}/N_n^2 \to 0$ as $n\to\infty$. Then it follows from Markov's inequality that

$$\frac{1}{N_n} \sum_{i \in [N_n]} \left(Z_{ij,n} - E\{Z_{ij,n}\} \right) \stackrel{p}{\to} 0$$

for each $j \in [J]$. In other words, for any positive number ξ and events

$$A_{j,n} := \left| \frac{1}{N_n} \sum_{i \in [N_n]} (Z_{ij,n} - E\{Z_{ij,n}\}) \right| \le \xi,$$

we have $\lim_{n\to\infty} P(A_{j,n}) = 1$. Combined with $E\{Z_{ij,n}\} \geq c_j$, we have, under $A_{j,n}$ with $\xi \leq c_j/2$,

$$\frac{1}{N_n} \sum_{i \in [N_n]} \log\{1 + u\left(h_{r_{i,n},Q}(X_{i,n})/h_{r_{i,n},\mathcal{B}_j}(X_{i,n}) - 1\right)\} > c_j/2,$$

and hence

$$0 < \sum_{i \in [N_n]} \log\{1 + u\left(h_{r_{i,n},Q}(X_{i,n})/h_{r_{i,n},\mathcal{B}_j}(X_{i,n}) - 1\right)\}$$

$$\leq \inf_{Q' \in \mathcal{B}_j} \sum_{i \in [N_n]} \log\{1 + u\left(h_{r_{i,n},Q}(X_{i,n})/h_{r_{i,n},Q'}(X_{i,n}) - 1\right)\}$$

for each $j \in [J]$. Noting that $\mathcal{B}_{\delta}^{c}(Q) \subset \bigcup_{j=1}^{J} \mathcal{B}_{j}$, the last display implies that under events $A_{n} := \bigcap_{j \in [J]} A_{j,n}$ with $\xi \leq \min_{j \in [J]} c_{j}/2$ we have

$$0 < \inf_{Q' \notin \mathcal{B}_{\delta}(Q)} \sum_{i \in [N_n]} \log \{ 1 + u \left(h_{r_{i,n},Q}(X_{i,n}) / h_{r_{i,n},Q'}(X_{i,n}) - 1 \right) \},$$

or equivalently,

$$l_n(uQ + (1-u)Q') > l_n(Q')$$

for all $Q' \in \mathcal{B}_{\delta}^{c}(Q)$, where for each $Q' \in \mathbb{Q}_{B}$

$$l_n(Q') := \sum_{i \in [N_n]} \log \int_0^B e^{-r_{i,n}\lambda} \frac{(r_{i,n}\lambda)^{X_{i,n}}}{X_{i,n}!} dQ'(\lambda).$$

Therefore, under events A_n with $\xi \leq \min_{j \in [J]} c_j/2$, the maximum likelihood estimator \widehat{Q} must belong to $\mathcal{B}_{\delta}(Q)$ and hence $W_1(\widehat{Q},Q) \leq \delta$. Since $P(A_n) \to 1$, we have $P(W_1(\widehat{Q},Q) \leq \delta) \to 1$, or equivalently, $W_1(\widehat{Q},Q) \stackrel{p}{\to} 0$ as $n \to \infty$. It further follows from $W_1(\widehat{Q},Q) \leq B$ that $E\{W_1(\widehat{Q},Q)\} \to 0$ as $n \to \infty$.

Step 2. For any $Q_0 \in \mathbb{Q}_B$, it follows from **Step 1** that

$$E\{W_1(\widehat{Q}, Q) \mid Q = Q_0\} = E\{W_1(\widehat{Q}, Q_0) \mid Q = Q_0\} = E\{W_1(\widehat{Q}, Q_0)\} \to 0,$$

where the expectation in the last term $E\{W_1(\widehat{Q},Q_0)\}$ is with respect to the randomness from the "measurement model" (1.1) and "expression model" (1.2) only. Then it follows from $P(Q \in \mathbb{Q}_B) = 1$ that $E\{W_1(\widehat{Q},Q) \mid Q\} \to 0$ for almost all Q with regard to the measure Q.

Proof of Theorem 2.3. By the construction of the population model (2.1), under the H_0 in (2.3) $Q_j^{(k)}$'s are independent and identically distributed. Furthermore, since the sets $\{r_{ij}^{(k)}, i \in [N]\}$ are invariant with respect to $j \in [n_k]$ and $k \in [K]$ for each $i \in [N]$, the random vectors $(X_{1j}^{(k)}, \ldots, X_{Nj}^{(k)})^{\top}$'s are independent and identically distributed. Therefore, $\widetilde{Q}_j^{(k)}$'s are independent and identically distributed. As a consequence, \widetilde{F} is uniformly distributed over

$$\widetilde{\mathcal{F}}^{\pi} := \left\{ \widetilde{F}^{\pi} : \pi \in \text{ all permutations of } [n] \to [n] \right\}$$

and hence

$$P(\widetilde{F} > \text{ the } 1 - \alpha \text{ quantile of } \widetilde{\mathcal{F}}^{\pi} \mid H_0) \leq \alpha.$$

Note that the event

$$\widetilde{F} >$$
 the $1 - \alpha$ quantile of $\widetilde{\mathcal{F}}^{\pi}$

is identical to the event

 $P(\widetilde{F}^{\pi} < \widetilde{F} \mid \widetilde{Q}_{j}^{(k)})$'s) $\geq 1 - \alpha$, where probability here is with respect to the random permutation π , and hence $P(\widetilde{T}_{\alpha} = 1 \mid H_{0}) \leq \alpha$. The proof of $P(\widetilde{T}_{h,\alpha} = 1 \mid H_{0}) \leq \alpha$ is analogous and hence omitted. \square

Proposition 7.1. Suppose P and Q are two distributions supported on $[0, \infty)$. Then $W_1(P, Q) \leq E\{P\} + E\{Q\}$ and $W_1(P, Q) \geq |E\{P\} - E\{Q\}|$.

Proof. Denote distribution functions of P and Q by F_P and F_Q respectively. Then it follows from the triangle inequality that $W_1(P,Q) = \int_0^\infty |(1-F_P) - (1-F_Q)| \le \int_0^\infty (1-F_P) + \int_0^\infty (1-F_Q) = E\{P\} + E\{Q\}$ and $W_1(P,Q) = \int_0^\infty |(1-F_P) - (1-F_Q)| \ge |E\{P\} - E\{Q\}|$.

Define

$$F := \left(SS_T - \sum_{k \in [K]} SS_k \right) / \sum_{k \in [K]} SS_k, \tag{7.1}$$

where

$$SS_T := \frac{1}{n} \sum_{k_1, k_2 \in [K]} \sum_{j_1 \in [n_{k_1}], j_2 \in [n_{k_2}]} W_1(Q_{j_1}^{(k_1)}, Q_{j_2}^{(k_2)})^2 \quad \text{and} \quad SS_k := \frac{1}{n_k} \sum_{j_1, j_2 \in [n_k]} W_1(Q_{j_1}^{(k)}, Q_{j_2}^{(k)})^2.$$

For any permutation $\pi:[n]\to[n]$, define

$$F^{\pi} := \left(SS_T - \sum_{k \in [K]} SS_k^{\pi} \right) / \sum_{k \in [K]} SS_k^{\pi}, \tag{7.2}$$

where

$$SS_k^{\pi} := \frac{1}{n_k} \sum_{j_1, j_2 \in [n_k]} W_1 \left(Q_{\Pi_1^{j_1, k}}^{(\Pi_2^{j_1, k})}, Q_{\Pi_1^{j_2, k}}^{(\Pi_2^{j_2, k})} \right)^2 \text{ for each } k \in [K].$$

Proof of Theorem 2.4(a). Throughout this proof, unless conditioning on certain events, the probability refers to randomness from all three layers as well as the permutation. Without loss of generality, it is assumed that Q_k is non-degenerate for each $k \in [K]$. Otherwise, the proof is analogous and omitted.

This proof consists of five steps. In the first step, we prove that if the following Equation (7.3) is true,

$$\lim_{n \to \infty} P(\widetilde{F} > \widetilde{F}^{\pi} | H_1) = 1, \tag{7.3}$$

then $\lim_{n\to\infty} P(\widetilde{T}_{\alpha} = 1 \mid H_1) = 1$ for any $\alpha \in (0,1)$. The rest four steps are devoted to proving Equation (7.3). Note that $\widetilde{F} - \widetilde{F}^{\pi} = (\widetilde{F} - F) + (F - F^{\pi}) + (F^{\pi} - \widetilde{F}^{\pi})$, where F is defined in (7.1) and F^{π} is defined in (7.2). The second step proves that $\widetilde{F} - F \xrightarrow{p} 0$ as $n \to \infty$. The third step proves that $F^{\pi} - \widetilde{F}^{\pi} \xrightarrow{p} 0$ as $n \to \infty$. The fourth step proves that $F - F^{\pi} \xrightarrow{p}$ some strictly positive constant. In the fifth step, we combine results in Steps 2-4 to prove (7.3) and hence finish the proof of Theorem 2.4(a).

In the following the notion H_1 in the probability is abandoned as long as no confusion is possible.

Step 1. Note that

$$P(\widetilde{T}_{\alpha} = 1) = P\Big\{P(\widetilde{F}^{\pi} < \widetilde{F} \mid \widetilde{Q}_{j}^{(k)}, \mathbf{s}) \ge 1 - \alpha\Big\} = 1 - P\Big\{P(\widetilde{F}^{\pi} < \widetilde{F} \mid \widetilde{Q}_{j}^{(k)}, \mathbf{s}) < 1 - \alpha\Big\},$$

$$P\Big\{P(\widetilde{F}^{\pi} < \widetilde{F} \mid \widetilde{Q}_{j}^{(k)}, \mathbf{s}) < 1 - \alpha\Big\} = P\Big\{P(\widetilde{F}^{\pi} \ge \widetilde{F} \mid \widetilde{Q}_{j}^{(k)}, \mathbf{s}) > \alpha)\Big\} \le \frac{E\Big\{P(\widetilde{F}^{\pi} \ge \widetilde{F} \mid \widetilde{Q}_{j}^{(k)}, \mathbf{s})\Big\}}{\alpha},$$
 and

$$E\Big\{P(\widetilde{F}^{\pi} \geq \widetilde{F} \mid \widetilde{Q}_{j}^{(k)}\text{,s})\Big\} = P(\widetilde{F}^{\pi} \geq \widetilde{F}) = 1 - P(\widetilde{F}^{\pi} < \widetilde{F})$$

Therefore, we have $\lim_{n\to\infty} P\{P(\widetilde{F}^{\pi}<\widetilde{F}\mid \widetilde{Q}_{j}^{(k)},\mathbf{s})<1-\alpha\}=0$ and hence $\lim_{n\to\infty} P(\widetilde{T}_{\alpha}=1)=1$ as long as (7.3) holds.

Step 2. In this step, we prove that $\widetilde{F} - F \stackrel{p}{\to} 0$ as $n \to \infty$, where the probability here refers to randomness from all three layers.

Note that

$$\left|\widetilde{F} - F\right| = \left|\frac{\widetilde{SS}_T - \sum\limits_{k \in [K]} \widetilde{SS}_k}{\sum\limits_{k \in [K]} \widetilde{SS}_k} - \frac{SS_T - \sum\limits_{k \in [K]} SS_k}{\sum\limits_{k \in [K]} SS_k}\right| = \left|\frac{SS_T}{\sum\limits_{k \in [K]} SS_k} - \frac{\widetilde{SS}_T}{\sum\limits_{k \in [K]} SS_k} + \frac{\widetilde{SS}_T}{\sum\limits_{k \in [K]} SS_k} - \frac{\widetilde{SS}_T}{\sum\limits_{k \in [K]} \widetilde{SS}_k}\right|,$$

where SS_k and SS_T are defined in (7.1). It then follows from the triangle inequality that

$$\left| \widetilde{F} - F \right| \leq \left| \frac{SS_T - \widetilde{SS}_T}{\sum\limits_{k \in [K]} SS_k} \right| + \left| \frac{\widetilde{SS}_T}{\sum\limits_{k \in [K]} \widetilde{SS}_k} \right| \left| \frac{\sum\limits_{k \in [K]} (\widetilde{SS}_k - SS_k)}{\sum\limits_{k \in [K]} SS_k} \right|$$

$$\leq \left| \frac{SS_T - \widetilde{SS}_T}{\sum\limits_{k \in [K]} SS_k} \right| + \left| \frac{B^2}{\frac{1}{n-1} \sum\limits_{k \in [K]} \widetilde{SS}_k} \right| \left| \frac{\sum\limits_{k \in [K]} (\widetilde{SS}_k - SS_k)}{\sum\limits_{k \in [K]} SS_k} \right|, \tag{7.4}$$

where $\frac{1}{n-1}\widetilde{SS}_T \leq B^2$ follows from $W_1(\widetilde{Q}_{j_1}^{(k_1)}, \widetilde{Q}_{j_2}^{(k_2)}) \leq B^2$ for each j_1, j_2, k_1, k_2 . Step 2(a). We first prove that $\left|\frac{\widetilde{SS}_k}{n_k-1} - \frac{SS_k}{n_k-1}\right| \stackrel{p}{\to} 0$ and $\frac{1}{n-1}\left|\widetilde{SS}_T - SS_T\right| \stackrel{p}{\to} 0$. It follows from the triangle inequality that for each $k \in [K]$

$$\left| \frac{\widetilde{SS}_k}{n_k - 1} - \frac{SS_k}{n_k - 1} \right| = \frac{1}{n_k(n_k - 1)} \left| \sum_{j_1, j_2 \in [n_k]} \left(W_1(\widetilde{Q}_{j_1}^{(k)}, \widetilde{Q}_{j_2}^{(k)})^2 - W_1(Q_{j_1}^{(k)}, Q_{j_2}^{(k)})^2 \right) \right|$$

$$\leq \frac{2B}{n_k(n_k - 1)} \sum_{j_1, j_2 \in [n_k]} \left(W_1(\widetilde{Q}_{j_1}^{(k)}, Q_{j_1}^{(k)}) + W_1(\widetilde{Q}_{j_2}^{(k)}, Q_{j_2}^{(k)}) \right) \cdot I(j_1 \neq j_2)$$

$$= \frac{4B}{n_k} \sum_{j \in [n_k]} W_1(\widetilde{Q}_j^{(k)}, Q_j^{(k)})$$

and analogously we have

$$\left| \frac{\widetilde{SS}_T}{n-1} - \frac{SS_T}{n-1} \right| \le \frac{4B}{n} \sum_{k \in [K]} \sum_{j \in [n_k]} W_1(\widetilde{Q}_j^{(k)}, Q_j^{(k)}).$$

Therefore,

$$E\left\{\left|\frac{\widetilde{SS}_k}{n_k - 1} - \frac{SS_k}{n_k - 1}\right|\right\} \le 4B \cdot \frac{1}{n_k} \sum_{j \in [n_k]} E\left\{W_1(\widetilde{Q}_j^{(k)}, Q_j^{(k)})\right\} = 4B \cdot E\left\{W_1(\widetilde{Q}_1^{(k)}, Q_1^{(k)})\right\},$$

where the last equality follows from Assumption 2.1. Noting that $W_1(\widetilde{Q}_1^{(k)}, Q_1^{(k)}) \leq B$ and

$$E\left\{W_1(\widetilde{Q}_1^{(k)}, Q_1^{(k)}) \mid Q_1^{(k)}\right\} \stackrel{a.s.}{\to} 0,$$

we have using

$$E\left\{W_1(\widetilde{Q}_1^{(k)}, Q_1^{(k)})\right\} = E\left[E\{W_1(\widetilde{Q}_1^{(k)}, Q_1^{(k)})|Q_1^{(k)}\}\right]$$

that

$$E\left\{W_1(\widetilde{Q}_1^{(k)}, Q_1^{(k)})\right\} \to 0 \text{ as } n \to \infty.$$

Analogously, we have $E\left\{\frac{\left|\widetilde{SS}_{T}-SS_{T}\right|}{n-1}\right\}\to 0$ as $n\to\infty$. Therefore, in (7.4) we have $\frac{\left|\widetilde{SS}_{T}-SS_{T}\right|}{n-1}\to 0$ and $\sum_{k\in[K]}\frac{\left|\widetilde{SS}_{k}-SS_{k}\right|}{n_{k}-1}\stackrel{p}{\to} 0$.

Step 2(b). We then prove that $\frac{1}{n_k-1}SS_k \xrightarrow{p}$ some strictly positive constant.

It follows from $|W_1(Q_{j_1}^{(k_1)}, Q_{j_2}^{(k_2)})| \leq B$ and the strong law of large numbers for U-statistics Serfling (1980, Chapter 5.4) that

$$\frac{1}{n_k - 1} SS_k \stackrel{a.s.}{\to} E\{W_1(Q_1^{(k)}, Q_2^{(k)})^2\}. \tag{7.5}$$

If $E\{W_1(Q_1^{(k)},Q_2^{(k)})^2\}=0$, then $W_1(Q_1^{(k)},Q_2^{(k)})=0$ almost surely and hence $Q_1^{(k)}=Q_2^{(k)}$ almost surely, which implies that Q_k is degenerate.

Step 2(c). Built on Step 2(a) and Step 2(b), we have

$$\frac{1}{n_k-1}\widetilde{SS}_k = \frac{1}{n_k-1}(\widetilde{SS}_k - SS_k) + \frac{1}{n_k-1}SS_k \overset{p}{\to} E\Big\{W_1(Q_1^{(k)},Q_2^{(k)})^2\Big\}.$$

Therefore, Slutsky's theorem guarantees $|\widetilde{F} - F| \xrightarrow{p} 0$, where the probability here refers to randomness from all three layers.

Step 3. In this step, we prove that $F^{\pi} - \tilde{F}^{\pi} \stackrel{p}{\to} 0$ as $n \to \infty$, where the probability here refers to randomness from all three layers as well as the permutation.

To prove it, it suffices to show that $\frac{1}{n_k-1}\left|\widetilde{SS}_k^{\pi}-SS_k^{\pi}\right| \xrightarrow{p} 0$ and $\frac{1}{n_k-1}SS_k^{\pi} \xrightarrow{p}$ some strictly positive constant since

$$\left| \widetilde{F}^{\pi} - F^{\pi} \right| \le \left| \frac{SS_T - \widetilde{SS}_T}{\sum\limits_{k \in [K]} SS_k^{\pi}} \right| + \left| \frac{B^2}{\frac{1}{n-1} \sum\limits_{k \in [K]} \widetilde{SS}_k^{\pi}} \right| \left| \frac{\sum\limits_{k \in [K]} (\widetilde{SS}_k^{\pi} - SS_k^{\pi})}{\sum\limits_{k \in [K]} SS_k^{\pi}} \right|, \tag{7.6}$$

where SS_k^{π} and SS_T^{π} are defined in (7.2).

Step 3(a). We first prove $\frac{1}{n_k-1} \left| \widetilde{SS}_k^{\pi} - SS_k^{\pi} \right| \stackrel{p}{\to} 0$.

To prove it, note that with similar arguments in Step 2(a) we have

$$E\left\{\left|\frac{\widetilde{SS}_{k}^{\pi}}{n_{k}-1} - \frac{SS_{k}^{\pi}}{n_{k}-1}\right|\right\} \leq 4B \cdot \frac{1}{n_{k}} \sum_{j \in [n_{k}]} E\left\{W_{1}(\widetilde{Q}_{\Pi_{1}^{j,k}}^{(\Pi_{2}^{j,k})}, Q_{\Pi_{1}^{j,k}}^{(\Pi_{2}^{j,k})})\right\}.$$

Let $n_{k,k'}^{\pi}$ represent the number of indices exchanged between group k and k' after the specific permutation π . Note that $n_{k,k'}^{\pi} = n_{k',k}^{\pi}$ and $\sum_{k'} n_{k,k'}^{\pi} = n_k$. Then, with the aid of the notations $\{n_{k,k'}^{\pi}\}$, it follows that

$$\sum_{j \in [n_k]} E\left\{ W_1(\widetilde{Q}_{\Pi_1^{j,k}}^{(\Pi_2^{j,k})}, Q_{\Pi_1^{j,k}}^{(\Pi_2^{j,k})}) \middle| \pi \right\} = \sum_{k' \in [K]} \sum_{j \in [n_{k,k'}]} E\left\{ W_1(\widetilde{Q}_j^{(k')}, Q_j^{(k')}) \middle| \pi \right\}$$

$$= \sum_{k' \in [K]} n_{k,k'}^{\pi} E\left\{ W_1(\widetilde{Q}_1^{(k')}, Q_1^{(k')}) \right\}$$

and hence

$$\sum_{j \in [n_k]} E\left\{\frac{W_1(\widetilde{Q}_{\Pi_1^{j,k}}^{(\Pi_2^{j,k})}, Q_{\Pi_1^{j,k}}^{(\Pi_2^{j,k})})}{n_k}\right\} = \sum_{k' \in [K]} E\left\{W_1(\widetilde{Q}_1^{(k')}, Q_1^{(k')})\right\} E\left\{\frac{n_{k,k'}^\pi}{n_k}\right\} = \sum_{k' \in [K]} E\left\{\frac{W_1(\widetilde{Q}_1^{(k')}, Q_1^{(k')})}{K}\right\}.$$

Therefore, it follows from $E\left\{W_1(\widetilde{Q}_1^{(k')}, Q_1^{(k')})\right\} \to 0$ for each $k \in [K]$ that $E\left\{\left|\frac{\widetilde{SS}_k^{\pi}}{n_k - 1} - \frac{SS_k^{\pi}}{n_k - 1}\right|\right\} \to 0$.

Step 3(b). We then prove $\frac{1}{n_k-1}SS_k^{\pi} \xrightarrow{p}$ some strictly positive constant.

To prove it, let $X \stackrel{d}{=} Y$ denote that the two random variables X, Y are identically distributed and note that

$$\frac{SS_{k}^{\pi}}{n_{k}-1} \stackrel{d}{=} \sum_{k' \in [K]} \sum_{\substack{j_{1},j_{2} \in [n_{k,k'}^{\pi}]}} \frac{W_{1}(Q_{j_{1}}^{(k')},Q_{j_{2}}^{(k')})^{2}}{n_{k}(n_{k}-1)} + \sum_{\substack{k'_{1} \neq k'_{2} \in [K]}} \sum_{\substack{j_{1} \in [n_{k,k'_{1}}^{\pi}],j_{2} \in [n_{k,k'_{2}}^{\pi}]}} \frac{W_{1}(Q_{j_{1}}^{(k'_{1})},Q_{j_{2}}^{(k'_{2})})^{2}}{n_{k}(n_{k}-1)}.$$
 (7.7)

(i) We first prove that the variance of (a) converges to 0.

Note that the variance of (a) equals to

$$\operatorname{Var}\left\{E\left\{\sum_{j_{1},j_{2}\in[n_{k,k'}^{\pi}]}\frac{W_{1}(Q_{j_{1}}^{(k')},Q_{j_{2}}^{(k')})^{2}}{n_{k}(n_{k}-1)}\Big|\pi\right\}\right\}+E\left\{\operatorname{Var}\left\{\sum_{j_{1},j_{2}\in[n_{k,k'}^{\pi}]}\frac{W_{1}(Q_{j_{1}}^{(k')},Q_{j_{2}}^{(k')})^{2}}{n_{k}(n_{k}-1)}\Big|\pi\right\}\right\},$$

where the first term equals to

$$\operatorname{Var}\left\{\frac{n_{k,k'}^{\pi}(n_{k,k'}^{\pi}-1)}{n_k(n_k-1)}E\{W_1(Q_1^{(k')},Q_2^{(k')})^2\}\right\} \leq B^4 \cdot \operatorname{Var}\left\{\frac{n_{k,k'}^{\pi}(n_{k,k'}^{\pi}-1)}{n_k(n_k-1)}\right\}.$$

For the second term, note that

$$\operatorname{Var}\left\{ \sum_{j_1 \neq j_2 \in [n_{k,k'}^{\pi}]} W_1(Q_{j_1}^{(k')}, Q_{j_2}^{(k')})^2 \mid \pi \right\}$$

$$= \sum_{j_1 \neq j_2 \in [n_{k,k'}^{\pi}]} \sum_{j'_1 \neq j'_2 \in [n_{k,k'}^{\pi}]} \operatorname{Cov} \left\{ W_1(Q_{j_1}^{(k')}, Q_{j_2}^{(k')})^2, W_1(Q_{j'_1}^{(k')}, Q_{j'_2}^{(k')})^2 \right\}$$

$$\leq B^4 \sum_{j_1 \neq j_2 \in [n_{k,k'}^{\pi}]} \sum_{j'_1 \neq j'_2 \in [n_{k,k'}^{\pi}]} I \left(\text{At least two of } \{j_1, j_2, j'_1, j'_2\} \text{ are identical.} \right)$$

$$\leq B^4 \cdot 2n_{k,k'}^{\pi} (n_{k,k'}^{\pi} - 1)^2.$$

Therefore, the variance of (a) is upper bounded by

$$\frac{2B^4}{(n_k(n_k-1))^2} \left[\operatorname{Var} \{ n_{k,k'}^{\pi} (n_{k,k'}^{\pi} - 1) \} + E \left\{ (n_{k,k'}^{\pi})^3 \right\} \right] \to 0,$$

where the convergence follows from $n_{k,k'}^{\pi}/n_k \stackrel{p}{\to} 1/K$, $n_{k,k'}^{\pi}/n_k \leq 1$, the dominated convergence theorem such that

$$E\{(n_{k,k'}^{\pi})^3\}/(n_k(n_k-1))^2 \to E\{0\} = 0,$$

and

$$\frac{\operatorname{Var}\{n_{k,k'}^{\pi}(n_{k,k'}^{\pi}-1)\}}{(n_k(n_k-1))^2} = E\left\{\left(\frac{n_{k,k'}^{\pi}(n_{k,k'}^{\pi}-1)}{n_k(n_k-1)}\right)^2\right\} - \left(E\left\{\frac{n_{k,k'}^{\pi}(n_{k,k'}^{\pi}-1)}{n_k(n_k-1)}\right\}\right)^2 \to \frac{1}{K^4} - \frac{1}{K^4} = 0.$$

To prove $n_{k,k'}^{\pi}/n_k \stackrel{p}{\to} 1/K$, note that $E\{n_{k,k'}^{\pi}/n_k\} = 1/K$ and $Var\{n_{k,k'}^{\pi}/n_k\} = Var\{n_{1,1}^{\pi}/n_1\} = \frac{n_1^2(n-n_1)^2}{n_1^2n^2(n-1)} \to 0$ (cf. Chapuy (2007, page 460)).

(ii) We then prove that the expectation of (a) converges to $E\left\{W_1(Q_1^{(k')},Q_2^{(k')})^2\right\}/K^2$. For this, we have

$$E\{(a)\} = E\left\{\frac{1}{n_k(n_k - 1)} \sum_{j_1, j_2 \in [n_{k,k'}^{\pi}]} E\left\{W_1(Q_{j_1}^{(k')}, Q_{j_2}^{(k')})^2 | \pi\right\}\right\}$$
$$= E\left\{\frac{n_{k,k'}^{\pi}(n_{k,k'}^{\pi} - 1)}{n_k(n_k - 1)} E\left\{W_1(Q_1^{(k')}, Q_2^{(k')})^2\right\}\right\},$$

which converges to $E\left\{W_1(Q_1^{(k')},Q_2^{(k')})^2\right\}/K^2$ by the dominated convergence theorem.

(iii) Built on (i) and (ii), it follows from Markov's inequality that (a) $\stackrel{p}{\to} E\left\{W_1(Q_1^{(k')},Q_2^{(k')})^2\right\}/K^2$. Analogously, we can prove that the second term in (7.7) converges to a constant in probability, i.e.,

$$\sum_{k_1' \neq k_2' \in [K]} \frac{1}{n_k(n_k-1)} \sum_{j_1 \in [n_{k,k_1'}^\pi], j_2 \in [n_{k,k_2'}^\pi]} W_1(Q_{j_1}^{(k_1')}, Q_{j_2}^{(k_2')})^2 \xrightarrow{p} \sum_{k_1' \neq k_2' \in [K]} \frac{E\{W_1(Q_1^{(k_1')}, Q_1^{(k_2')})^2\}}{K^2}.$$

As a result, we have

$$\frac{1}{n_k - 1} S S_k^{\pi} \xrightarrow{p} \sum_{k' \in [K]} \frac{E\left\{W_1(Q_1^{(k')}, Q_2^{(k')})^2\right\}}{K^2} + \sum_{k'_1 \neq k'_2 \in [K]} \frac{E\left\{W_1(Q_1^{(k'_1)}, Q_1^{(k'_2)})^2\right\}}{K^2} > 0.$$
 (7.8)

Step 4. In this step we prove that $F - F^{\pi} \stackrel{p}{\to}$ some strictly positive constant, where the probability

here refers to randomness from all three layers and permutations.

To prove it, note that

$$F - F^{\pi} = \frac{SS_T}{\sum_{k \in [K]} SS_k} - \frac{SS_T}{\sum_{k \in [K]} SS_k^{\pi}} = \frac{1}{n-1} SS_T \left(\frac{1}{\frac{1}{n-1} \sum_{k \in [K]} SS_k} - \frac{1}{\frac{1}{n-1} \sum_{k \in [K]} SS_k^{\pi}} \right).$$

Step 4(a). We first prove that $\frac{1}{n-1}SS_T \stackrel{p}{\to}$ some strictly positive constant. Note that

$$\frac{1}{n-1}SS_{T} = \frac{1}{n(n-1)} \sum_{k_{1},k_{2} \in [K]} \sum_{j_{1} \in [n_{k_{1}}],j_{2} \in [n_{k_{2}}]} W_{1} \left(Q_{j_{1}}^{(k_{1})},Q_{j_{2}}^{(k_{2})}\right)^{2}$$

$$= \sum_{k_{1},k_{2} \in [K]} \frac{n_{k_{1}}n_{k_{2}}}{n(n-1)} \frac{1}{n_{k_{1}}n_{k_{2}}} \sum_{j_{1} \in [n_{k_{1}}],j_{2} \in [n_{k_{2}}]} W_{1} \left(Q_{j_{1}}^{(k_{1})},Q_{j_{2}}^{(k_{2})}\right)^{2}$$

$$\stackrel{p}{\to} \frac{1}{K^{2}} \sum_{k_{1},k_{2} \in [K]} E\left\{W_{1}(Q_{1}^{(k_{1})},Q_{2}^{(k_{2})})^{2}\right\} > 0,$$

which follows from the strong law of large numbers for U-statistics Serfling (1980, Chapter 5.4).

Step 4(b). Build on Step 3(a), (7.5), and (7.8), it suffices to prove that $\sum_{k \in [K]} \frac{1}{n-1} (SS_k - SS_k^{\pi}) \stackrel{p}{\to}$

some strictly negative constant. It follows from (7.5) and (7.8) that

$$\sum_{k \in [K]} \frac{1}{n_k - 1} (SS_k - SS_k^{\pi})$$

$$\stackrel{p}{\to} \left(1 - \frac{1}{K} \right) \sum_{k \in [K]} E\{W_1(Q_1^{(k)}, Q_2^{(k)})^2\} - \sum_{k_1' \neq k_2' \in [K]} \frac{E\{W_1(Q_1^{(k_1')}, Q_1^{(k_2')})^2\}}{K}$$

$$= (K - 1) \left(\frac{1}{K} \sum_{k \in [K]} E\{W_1(Q_1^{(k)}, Q_2^{(k)})^2\} - \sum_{k_1' \neq k_2' \in [K]} \frac{E\{W_1(Q_1^{(k_1')}, Q_1^{(k_2')})^2\}}{K(K - 1)} \right) < 0,$$

where the last inequality follows from H_1 and hence

$$\sum_{k \in [K]} \frac{1}{n-1} (SS_k - SS_k^{\pi}) \xrightarrow{p} \frac{K-1}{K} \left(\frac{1}{K} \sum_{k \in [K]} E\{W_1(Q_1^{(k)}, Q_2^{(k)})^2\} - \sum_{k_1' \neq k_2' \in [K]} \frac{E\{W_1(Q_1^{(k_1')}, Q_1^{(k_2')})^2\}}{K(K-1)} \right),$$

which is a strictly negative constant.

Step 5. Building on the previous three steps, we have established that $\widetilde{F} - \widetilde{F}^{\pi} \stackrel{p}{\to} C$, where C is a strictly positive constant. Accordingly, we have $\lim_{n\to\infty} P(\widetilde{F} > \widetilde{F}^{\pi} \mid H_1) = 1$.

Proof of Theorem 2.4(b). Noting Theorem 2.1 and Proposition 7.1, this is analogous to the proof of Theorem 2.4(a) and hence omitted. \Box

7.2 Proof of theorems in Section 3

Proof of Theorem 3.1. We focus on VDM. After understanding the proof of VDM, arguments for VEM and ISDM are straight-forward and hence omitted.

The proof of VDM largely remains the same as Böhning (1982) and we include it here only for the completeness of this paper. This proof consists of four steps. In the first step, we prove the existence of \widehat{Q} . In the second step, we prove an important property (7.9) for proving $\Phi(G_L) \to \Phi(\widehat{Q})$ as $L \to \infty$ if this algorithm doesn't stop. In the third step, we complete the proof in the case that this algorithm doesn't stop. In the fourth step, we complete the proof in the case that algorithm does stop at some L.

Step 1. This step gives a proof of the existence of \widehat{Q} , which is an analogue of Simar (1976, Section 3.1).

Let $\bar{\mathbb{Q}}_B$ be the set of all sub-distributions (total mass less or equal to 1) on [0, B] and let $\bar{\Gamma}_N := \{ \boldsymbol{\mu}(\bar{G}) | \bar{G} \in \bar{\mathbb{Q}}_B \}$, where $\bar{G} \mapsto \boldsymbol{\mu}(\bar{G}) := (\mu_1(\bar{G}), \dots, \mu_N(\bar{G}))$ and

$$\bar{G} \mapsto \mu_i(\bar{G}) := \int_0^B \exp(-\lambda r_i)(\lambda r_i)^{X_i} d\bar{G}(\lambda) \text{ for } i \in [N] \text{ and } \bar{G} \in \bar{\mathbb{Q}}_B.$$

We claim that $\bar{\Gamma}_N$ is convex and compact. Convexity is obvious. Compactness follows from the weak compactness of $\bar{\mathbb{Q}}_B$, boundedness and continuity of $\lambda \mapsto \exp(-\lambda r_i)(\lambda r_i)^{X_i}$ on [0, B], and Helly-Bray theorem, see Simar's arguments for further details. It further follows from the concavity of $(\mu_1, \ldots, \mu_N) \mapsto \Psi(\mu_1, \ldots, \mu_N) := \frac{1}{N} \sum_{i=1}^N \log \mu_i$ on $\bar{\Gamma}_N$ that there exists a unique maximizer $(\hat{\mu}_1, \ldots, \hat{\mu}_N)$ of Ψ on $\bar{\Gamma}_N$. By the construction of $\bar{\Gamma}_N$, there exists a sub-distribution $\bar{G}_{max} \in \bar{\mathbb{Q}}_B$ such that $(\hat{\mu}_1, \ldots, \hat{\mu}_N) = (\mu_1(\bar{G}_{max}), \ldots, \mu_N(\bar{G}_{max}))$. The proof of that \bar{G}_{max} is actually a distribution follows from exactly same arguments by Simar (1976, Page 1202). Now we complete the proof of the existence of \hat{Q} .

Step 2. Let \mathbb{Q}_B be the set of all distributions on [0, B] and let δ_{λ} be the deterministic distribution at $\lambda \in [0, B]$. Since we have $\Phi(G) > -\infty$ for each $G \in \mathbb{Q}_B \setminus \{\delta_0\}$, we can define the following directional directive

$$\Phi'(G, \delta_{\lambda}) := \lim_{\epsilon \to 0^{+}} \epsilon^{-1} \Big\{ \Phi\{(1 - \epsilon)G \oplus \epsilon \delta_{\lambda}\} - \Phi(G) \Big\} = \frac{1}{N} \sum_{i \in [N]} \frac{e^{-\lambda r_{i}} (\lambda r_{i})^{X_{i}}}{\mu_{i}(G)} - 1$$

for $G \in \mathbb{Q}_B \setminus \{\delta_0\}$ and $\lambda \in [0, B]$.

In the second step, we prove that for all $\nu > 0, \alpha \in \mathbb{R}$ there exists $\epsilon_0 = \epsilon_0(\nu, \alpha) \in (0, 1)$ such that

$$\Phi'(G, \delta_{\lambda}) \ge \nu \text{ implies } \Phi\{(1 - \epsilon)G \oplus \epsilon \delta_{\lambda}\} - \Phi(G) \ge \epsilon \nu/2$$
 (7.9)

for all $\epsilon \in [0, \epsilon_0(\nu, \alpha)]$, all $G \in \Delta_\alpha := \{G \in \mathbb{Q}_B | \Phi(G) \ge \alpha\}$, and all $\lambda \in [0, B]$.

 $\Psi, \mu, \bar{\mathbb{Q}}_B$ and $\bar{\Gamma}_N$ are defined in Step 1. Since Ψ is continuously differentiable on $\bar{\Gamma}_N \setminus \{0\}$, it follows from the mean value theorem that

$$\begin{split} \Phi\{(1-\epsilon)G \oplus \epsilon \delta_{\lambda}\} - \Phi(G) &= \Psi\{(1-\epsilon)\boldsymbol{\mu}(G) + \epsilon \boldsymbol{\mu}(\delta_{\lambda})\} - \Psi(\boldsymbol{\mu}(G)) \\ &= \epsilon \nabla \Psi\left\{(1-\xi\epsilon)\boldsymbol{\mu}(G) + \xi\epsilon \boldsymbol{\mu}(\delta_{\lambda})\right\}^T \boldsymbol{\mu}(\delta_{\lambda}) - 1, \end{split}$$

where $\nabla \Psi$ denotes the gradient of Ψ , for some $\xi \in [0,1]$. Therefore,

$$\Phi\{(1-\epsilon)G \oplus \epsilon\delta_{\lambda}\} - \Phi(G) - \epsilon\Phi'(G,\delta_{\lambda}) = \epsilon \left\{ \nabla\Psi\left\{(1-\xi\epsilon)\mu(G) + \xi\epsilon\mu(\delta_{\lambda})\right\} - \nabla\Psi(\mu(G)) \right\}^{T} \mu(\delta_{\lambda}).$$

Define $\mathcal{L}_{\alpha'} := \{ \boldsymbol{\mu} \in \bar{\Gamma}_N : \Psi \geq \alpha' \}$ for $\alpha' \in \mathbb{R}$. Note that $\mathcal{L}_{\alpha'}$ is a compact set, on which $\nabla \Psi$ is

uniformly continuous, for $\alpha' = \alpha - 1$. Since $\mu(G) \in \mathcal{L}_{\alpha}$, we can find a sufficiently small $\epsilon_0 = \epsilon_0(\alpha, \nu)$ such that for all $\epsilon \in [0, \epsilon_0]$ we have $(1 - \xi \epsilon)\mu(G) + \xi \epsilon \mu(\delta_{\lambda}) \in \mathcal{L}_{\alpha-1}$ and

$$\|\nabla \Psi \{(1 - \xi \epsilon) \boldsymbol{\mu}(G) + \xi \epsilon \boldsymbol{\mu}(\delta_{\lambda})\} - \nabla \Psi(\boldsymbol{\mu}(G))\| \le \nu/(2S),$$

where $\|\cdot\|$ denotes the Euclidean norm and $S:=\sup_{\mu\in\bar{\Gamma}_N}\|\mu\|$. Therefore we have

$$|\Phi\{(1-\epsilon)G \oplus \epsilon\delta_{\lambda}\} - \Phi(G) - \epsilon\Phi'(G,\delta_{\lambda})| \le \epsilon\nu/(2S) \cdot S = \epsilon\nu/2.$$
(7.10)

If the claim doesn't hold, i.e. $\Phi\{(1-\epsilon)G \oplus \epsilon\delta_{\lambda}\} - \Phi(G) < \epsilon\nu/2$, it follows from $-\Phi'(G,\delta_{\lambda}) \le -\nu$ that

$$\Phi\{(1-\epsilon)G \oplus \epsilon\delta_{\lambda}\} - \Phi(G) - \epsilon\Phi'(G,\delta_{\lambda}) < \epsilon\nu/2 - \epsilon\nu = -\epsilon\nu/2,$$

which contradicts (7.10).

Step 3. In this step, we assume that VDM doesn't stop and we have $\Phi(G_L) \to \Phi(\widehat{Q})$ as $L \to \infty$. Note that $\Phi(G_L)$ is monotonically increasing and suppose $\lim_{L\to\infty} \Phi(G_L) = \Phi^+$. If $\Phi^+ < \Phi(\widehat{Q})$, then we have

$$\Phi'(G_L, \delta_{\lambda_{\max}}) = \max_{\lambda \in [0, B]} \Phi'(G_L, \delta_{\lambda}) \ge \Phi'(G_L, \widehat{Q}) \ge \Phi(\widehat{Q}) - \Phi(G_L) \ge \Phi(\widehat{Q}) - \Phi^+ \ge \nu > 0,$$

for some $\nu > 0$, where the first inequality follows from Simar (1976, Page 1204) and the second inequality follows from the concavity of $\epsilon \mapsto \Phi((1-\epsilon)G_L + \epsilon \widehat{Q})$ with $\epsilon \in [0,1]$. Then it follows from the claim in Step 2 that

$$\Phi(G_{L+1}) - \Phi(G_L) \ge \Phi\{(1 - \epsilon_0)G_L \oplus \epsilon_0 \delta_{\lambda_{\max}}\} - \Phi(G_L) \ge \nu \epsilon_0/2 > 0,$$

which contradicts $\lim_{L\to\infty} \Phi(G_L) = \Phi^+$.

Step 4. In this step, we prove that if VDM stops at some L, then $\Phi(G_L) = \Phi(\widehat{Q})$.

If $\Phi(G_L) < \Phi(\widehat{Q})$, we then have

$$\max_{\lambda \in [0,B]} \Phi'(G_L, \delta_\lambda) \ge \Phi(\widehat{Q}) - \Phi(G_L) > 0,$$

which contradicts the criterion for stopping this algorithm.

7.3 Proof of theorems in Section 6

Proof of Theorem 6.1(a). This proof consists of two steps, similar to Section 4 in Vinayak et al. (2019). In the first step, we prove that $W_1(Q, \widehat{Q})$ can be upper bounded by three parts, see (7.11). In the second step, we upper bound these three parts separately with the help of Lemma A.1, Lemma A.2 and Proposition A.2 and complete this proof.

Step 1. For $x=0,1,\ldots$, let $x\mapsto h_Q^{obs}(x)$ denote the sample proportion, i.e. $h_Q^{obs}(x):=\sum_{i=1}^N I(x=X_i)/N$, where $I(\cdot)$ is an indicator function. Recall that $W_1(Q,\widehat{Q})=\sup_{\ell\in \operatorname{Lip}_1}\int_0^B\ell \operatorname{d}(Q-\widehat{Q})$, where Lip_1 represents all 1-Lipschitz functions on [0,B] and ℓ is one of those 1-Lipschitz functions. Without loss of generality, it is assumed that $\ell(0)=0$. The idea is to use the following function

$$\lambda \mapsto \widehat{\ell}(\lambda) := \sum_{x=0}^{\infty} b_x \frac{\lambda^x e^{-\lambda}}{x!}$$
, where $b_x \in \mathbb{R}$ and $\lambda \in [0, B]$,

to approximate the 1-Lipschitz function $\lambda \mapsto \ell(\lambda)$ and upper bound $W_1(Q,\widehat{Q})$ by three parts. It

follows from a straight-forward algebra that

$$\begin{split} \int_0^B \ell(\lambda) \mathrm{d} \left(Q(\lambda) - \widehat{Q}(\lambda) \right) &= \int_0^B \left(\ell(\lambda) - \widehat{\ell}(\lambda) \right) \mathrm{d} \left(Q(\lambda) - \widehat{Q}(\lambda) \right) + \int_0^B \sum_{x=0}^\infty b_x \frac{\lambda^x e^{-\lambda}}{x!} \mathrm{d} \left(Q(\lambda) - \widehat{Q}(\lambda) \right) \\ &\leq 2 \left\| \ell - \widehat{\ell} \right\|_\infty + \sum_{x=0}^\infty b_x \left(h_Q(x) - h_Q^{obs}(x) \right) + \sum_{x=0}^\infty b_x \left(h_Q^{obs}(x) - h_{\widehat{Q}}(x) \right), \end{split}$$

where $\|\ell-\widehat{\ell}\|_{\infty}:=\sup_{\lambda\in[0,B]}|\ell(\lambda)-\widehat{\ell}(\lambda)|,$ and hence

$$W_1(Q,\widehat{Q}) \le \sup_{\ell \in \text{Lip}(1)} \left(2 \left\| \ell - \widehat{\ell} \right\|_{\infty} + \sum_{x=0}^{\infty} b_x \left(h_Q(x) - h_Q^{obs}(x) \right) + \sum_{x=0}^{\infty} b_x \left(h_Q^{obs}(x) - h_{\widehat{Q}}(x) \right) \right). (7.11)$$

Step 2. It follows from Lemma A.1 and Lemma A.2 that for an arbitrary $\delta \in (0, 1/2)$ and an arbitrary $\epsilon \in (0, 1)$ there exists constants $N(\epsilon)$ and $C(\epsilon)$ depending only on ϵ such that the sum of the last two terms in (7.11) is upper bounded by $C(\epsilon) \max_{x \geq 0} |b_x| \sqrt{\frac{B \vee 1}{N^{1-\epsilon} \delta^{1+\epsilon}}}$ for all $N \geq N(\epsilon)$ with probability at least $1 - 2\delta$.

Step 2(a). Suppose $c_0 \leq \min \{ \sqrt{ec/C_2}, 0.001 \}$, where c = 1/8 and C_2 is a universal constant specified later. It follows from Proposition A.2(a) that $\ell(\lambda)$ can be approximated by $\widehat{\ell}(\lambda) = \sum_{x=0}^k b_x \frac{\lambda^x e^{-\lambda}}{x!}$ with an uniform approximation error of $C_1 B/k$ with $\max_x |b_x| \leq C_1 (\sqrt{ek/B})^k$ for $k \geq 4(B \vee 1)$, where $C_1 > 1$ is a universal constant. Hence we have

$$W_1(Q,\widehat{Q}) \le 2C_1 \frac{B}{k} + C_1 C(\epsilon) \left(\frac{\sqrt{ek}}{B}\right)^k \sqrt{\frac{B \vee 1}{N^{1-\epsilon}} \frac{1}{\delta^{1+\epsilon}}},$$

for $N \ge N(\epsilon)$ and $k \ge 4(B \lor 1)$ with probability at least $1 - 2\delta$. Taking k = k(N, B) satisfying $(\sqrt{e}k/B)^k = N^c$ for c = 1/8, it follows that

$$W_1(Q, \hat{Q}) \le 2C_1 B/k + C_1 C(\epsilon) N^{c+\epsilon/2-1/2} \sqrt{B/\delta^{1+\epsilon}}.$$
 (7.12)

To verify $k(N,B) \ge 4(B \vee 1)$, note that $(\sqrt{e}k/B)^k = N^c$ is equivalent to

$$\log \left(\sqrt{e}k/B \right) \exp \{ \log \left(\sqrt{e}k/B \right) \} = (\sqrt{e}c \log N)/B.$$

It further follows from $(\sqrt{ec} \log N)/B > 0$ that k(N,B), as the solution of $(\sqrt{ek}/B)^k = N^c$, can be written using the Lambert W function, i.e. $k(N,B) = \frac{B}{\sqrt{e}} \exp\left(W\left(\frac{\sqrt{ec} \log N}{B}\right)\right)$, where W is the Lambert W function. It follows from the expansion of W (see Wiki of Lambert W function),

$$W(x) = \log x - \log \log x + o(1)$$
, as $x \to \infty$,

that there exists a universal constant $C_2 > 0$ such that

$$\exp(W(x)) \ge \frac{1}{2} \frac{x}{\log x}$$
, for $x \ge C_2$.

It then follows from that $B \leq c_0 \log N$ and $c_0 \leq \sqrt{ec/C_2}$ that

$$\frac{\sqrt{e}c\log N}{B} \geq \frac{\sqrt{e}c\log N}{c_0\log N} \geq C_2$$

and hence

$$k(N,B) = \frac{B}{\sqrt{e}} \exp\left(W\left(\frac{\sqrt{ec\log N}}{B}\right)\right) \ge \frac{B}{2\sqrt{e}} \frac{\frac{\sqrt{ec\log N}}{B}}{\log \frac{\sqrt{ec\log N}}{B}} \ge \frac{c}{2} \frac{\log N}{\log \frac{\log N}{B}}.$$
 (7.13)

It further follows from $B \leq c_0 \log N$ with $c_0 \leq 0.001$ that

$$\frac{k(N,B)}{B} \ge \frac{c}{2} \frac{\log N}{B} / \log \frac{\log N}{B} \ge \frac{1}{16} \frac{1000}{\log 1000} \ge 4.$$

If $\frac{c}{2} \frac{\log N}{\log \frac{\log N}{B}} \ge 4$ doesn't hold, then $E\{W_1(Q, \widehat{Q})\} \le B \le \frac{64B}{\log N} \log \left(\frac{\log N}{B} \lor e\right)$ and hence Theorem 6.1(a) is trivial. Therefore without loss of generality we assume that $\frac{c}{2} \frac{\log N}{\log \frac{\log N}{B}} \ge 4$ and hence $k(N, B) \ge 4$. As a consequence, we have $k(N, B) \ge 4(B \lor 1)$.

Combining (7.12) with (7.13) and letting $\epsilon = 1/4$, we have

$$W_1(Q, \widehat{Q}) \le 32C_1 \frac{B \log \frac{\log N}{B}}{\log N} + C_1 C(\epsilon)|_{\epsilon = 1/4} \cdot N^{-1/4} \sqrt{\frac{B \vee 1}{\delta^{1+\epsilon}}},$$

where $C(\epsilon)|_{\epsilon=1/4}$ means the value of the function $\epsilon \mapsto C(\epsilon)$ at 1/4. Therefore, for an arbitrary $\delta \in (0, 1/2)$, there exists a universal constant C_3 such that for sufficiently large N we have

$$W_1(Q, \widehat{Q}) \le C_3 \frac{B}{\log N} \left(\log \frac{\log N}{B} \right) \frac{1}{\delta^{5/8}},$$

with probability at least $1-2\delta$. Therefore, for sufficiently large N we have

$$E\{W_1(Q,\widehat{Q})\} \le 5C_3 \frac{B}{\log N} \log \frac{\log N}{B} \le 5C_3 \frac{B}{\log N} \log \left(\frac{\log N}{B} \vee e\right).$$

Step 2(b). Suppose $c_0 > \min \left\{ \frac{\sqrt{ec}}{C_2}, 0.001 \right\}$. Then for $B \in [\min \left\{ \sqrt{ec}/C_2, 0.001 \right\} \log N, c_0 \log N \right]$, it follows from Theorem 6.1(b) that $E\{W_1(Q, \widehat{Q})\} \leq C_4 \sqrt{B/\log N} \leq C_4 \sqrt{c_0}$, where C_4 is a universal constant. On the other hand, in this case $\frac{B}{\log N} \log \left(\frac{\log N}{B} \vee e \right) \geq \min \left\{ \sqrt{ec}/C_2, 0.001 \right\}$ and hence

$$E\{W_1(Q,\widehat{Q})\} \le \max\left\{5C_3, \frac{C_4\sqrt{c_0}}{\min\left\{\sqrt{ec}/C_2, 0.001\right\}}\right\} \frac{B}{\log N} \log\left(\frac{\log N}{B} \vee e\right)$$

holds for all $B \leq c_0 \log N$.

Proof of Theorem 6.1(b). Since $B \geq c_0 \log N$, we have $B \geq 1$ for sufficiently large N. It follows from Step 1 in the proof of Theorem 6.1(a), Lemma A.1 and Lemma A.2 that for an arbitrary $\delta \in (0, 1/2)$ and an arbitrary $\epsilon \in (0, 1)$ there exist constants $N(\epsilon)$ and $C(\epsilon)$ depending only on ϵ such that the sum of the last two terms in (7.11) is upper bounded by $C(\epsilon) \max_{x \geq 0} |b_x| \sqrt{\frac{B}{N^{1-\epsilon}\delta^{1+\epsilon}}}$ for all $N \geq N(\epsilon)$ with probability at least $1-2\delta$.

If $c_0 \ge 100$, it follows further from Proposition A.2(b) that for sufficiently small ϵ there exists a constant $C_1 = C_1(\epsilon)$ such that

$$W_1(Q,\widehat{Q}) \le C_1 \left(\sqrt{\frac{B}{\log N}} + B^{3/2} N^{-1/2 + 2\epsilon} \sqrt{\frac{1}{\delta^{1+\epsilon}}} \right),$$

with probability at least $1-2\delta$. Since $B^3 \leq C_0^3 N^{1-3\epsilon_0}$, then it follows from choosing $\epsilon = (\epsilon_0/2) \wedge 0.01$ that there exists a constant $C_2 = C_2(\epsilon_0)$ such that

$$W_1(Q,\widehat{Q}) \le C_2 \sqrt{\frac{B}{\log N} \frac{1}{\delta^{1+\epsilon}}}$$
 and hence $E\{W_1(Q,\widehat{Q})\} \le C_3 \sqrt{\frac{B}{\log N}}$,

where $C_3 = C_3(\epsilon_0)$ is a constant.

If $c_0 < 100$, a 1-Lipschitz function on [0, B] can also be viewed as a Lipschitz function on $[0, 100 \log N]$ and hence it follows from letting $B = 100 \log N$ in Proposition A.2(b) that for sufficiently small ϵ there exists a constant $C_4 = C_4(\epsilon)$ such that with probability $1 - 2\delta$

$$W_1(Q,\widehat{Q}) \le C_4 \left(1 + \sqrt{B} N^{-1/2 + 2\epsilon} \log N \cdot \sqrt{\frac{1}{\delta^{1+\epsilon}}} \right) \le C_4 \left(1 + \sqrt{C_0} N^{-1/3 + 2\epsilon} \log N \cdot \sqrt{\frac{1}{\delta^{1+\epsilon}}} \right).$$

Therefore it follows from letting $\epsilon = 0.01$ that for sufficiently large N

$$E\{W_1(Q,\widehat{Q})\} \le 2C_4 \le \frac{2C_4}{\sqrt{c_0}} \sqrt{\frac{B}{\log N}},$$

where the last inequality follows from $B \geq c_0 \log N$.

Proof of Theorem 6.2(a). Suppose $a \ge M \ge 0$ are constants and P and Q are two random variables supported on [a-M,a+M] with $E\{P^j\}=E\{Q^j\},\ 0\le j\le L$. Existence of P and Q is guaranteed by Proposition 4.3 in Vinayak et al. (2019).

For $0 < B \le c_0 \log N$, setting $a = C_1 B$, M = B and

$$(L+1)/2 = Be^2/(2C_1) \cdot \exp(W(4C_1\log(N)/(e^2B))),$$

where $W(\cdot)$ is the Lambert W function, $C_1 = \max\{1, 4e^2c_0, C_2c_0e^2/4, C_3c_0e^2/4\}$ and C_2, C_3 are universal positive constants specified later. Since $W(x) = \log x - \log\log x + o(1)$ as $x \to \infty$, there exists a universal constant C_2 such that for $x \ge C_2$ we have $W(x) \ge \frac{1}{2}\log x$. Therefore, it follows from

$$4C_1 \frac{\log N}{e^2 B} \ge 4C_2 c_0 \frac{e^2}{4} \frac{\log N}{e^2 B} \ge 4C_2 c_0 \frac{e^2}{4} \frac{\log N}{e^2 c_0 \log N} = C_2$$

that

$$L+1 = \frac{Be^2}{C_1} \cdot \exp\{W(4C_1\log(N)/(e^2B))\} \geq \frac{Be^2}{C_1} \sqrt{4C_1\frac{\log N}{e^2B}} \geq \frac{Be^2}{C_1} \sqrt{4C_1\frac{\log N}{e^2c_0\log N}} \geq \frac{4Be^2}{C_1}.$$

By $(2eM)^2/a = (2eB)^2/(C_1B) = 4e^2B/C_1$, it follows that $L+1 \ge (2eM)^2/a$. Hence it follows from Proposition A.3 that

$$TV(P,Q) \le 2\left(\frac{eB}{\sqrt{C_1B(L+1)}}\right)^{L+1} = 2\left(\frac{e^2B}{2C_1(L+1)/2}\right)^{\frac{L+1}{2}} = 2N^{-2},$$

where the last equality follows from the definition of the Lambert W function (see the proof of Theorem 6.1(a) for details). It follows from the LeCam minimax lower bound that for $N \geq 3$

$$\inf_{\widetilde{Q}} \sup_{Q} E\{W_1(Q,\widetilde{Q})\} \ge \frac{1}{2}W_1(P,Q)(1-\text{TV}(P_N,Q_N)) \ge \frac{1}{2}W_1(P,Q)\left(1-2NN^{-2}\right) \ge \frac{1}{6}W_1(P,Q).$$

On the other hand, it follows from Proposition 4.3 in Vinayak et al. (2019) that $W_1(P,Q) \ge 2M/(2L) = B/L$. Since $W(x) = \log x - \log \log x + o(1)$ as $x \to \infty$, there exists a universal constant C_3 such that for $x \ge C_3$ we have $W(x) \le 1 + \log x - \log \log x$. Therefore, it follows from

$$4C_1 \frac{\log N}{e^2 B} \ge 4C_3 c_0 \frac{e^2}{4} \frac{\log N}{e^2 B} \ge 4C_3 c_0 \frac{e^2}{4} \frac{\log N}{e^2 c_0 \log N} = C_3$$

that

$$L \leq \frac{Be^2}{C_1} \cdot \exp\{W(4C_1\log(N)/(e^2B))\} \leq \frac{Be^3}{C_1} \frac{4C_1\log N}{e^2B} / \log \frac{4C_1\log N}{e^2B} = 4e\log N / \log \frac{4C_1\log N}{e^2B}.$$

Therefore,

$$\inf_{\widetilde{Q}} \sup_{Q} E\{W_1(Q,\widetilde{Q})\} \geq \frac{1}{6}W_1(P,Q) \geq \frac{1}{6}\frac{B}{4e\log N}\log \frac{4C_1\log N}{e^2B} \geq \frac{B}{24e\log N}\log \frac{16c_0\log N}{B}.$$

This completes the proof.

Proof of Theorem 6.2(b). Suppose $a \ge M \ge 0$ are constants and P and Q are two random variables supported on [a-M,a+M] with $E\{P^j\}=E\{Q^j\},\ 0\le j\le L$. Existence of P and Q is guaranteed by Proposition 4.3 in Vinayak et al. (2019).

For $B \ge c_0 \log N$, setting $a = c_1 B / \sqrt{c_0}$, $L = \log N$ and $M = c_1 \sqrt{B \log N}$ with $c_1 = 1/(4e^4 \sqrt{c_0})$. Note that

$$\frac{a}{M} = \frac{c_1 B / \sqrt{c_0}}{c_1 \sqrt{B \log N}} = \sqrt{\frac{B}{c_0 \log N}} \ge 1$$

and

$$\frac{(2eM)^2}{a} = \frac{4e^2c_1^2B\log N}{c_1B/\sqrt{c_0}} = \sqrt{c_0}4e^2c_1\log N = \frac{\sqrt{c_0}4e^2}{4e^4\sqrt{c_0}}\log N = \frac{1}{e^2}\log N \le 1 + \log N = L + 1.$$

Therefore, it follows from the LeCam minimax lower bound and Proposition A.3 that

$$\inf_{\widetilde{Q}} \sup_{Q} E\{W_{1}(Q, \widetilde{Q})\} \geq \frac{1}{2} W_{1}(P, Q) (1 - \text{TV}(P_{N}, Q_{N}))$$

$$\geq \frac{1}{2} W_{1}(P, Q) \left(1 - 2N \left(\frac{ec_{1} \sqrt{B \log N}}{\sqrt{c_{1} B(1 + \log N) / \sqrt{c_{0}}}} \right)^{1 + \log N} \right)$$

$$\geq \frac{1}{2} W_{1}(P, Q) \left(1 - \frac{1}{e} N^{-\log 2} \right) \geq \frac{3}{10} W_{1}(P, Q).$$

On the other hand, it follows from Proposition 4.3 in Vinayak et al. (2019) that

$$W_1(P,Q) \ge \frac{2M}{2L} = \frac{c_1\sqrt{B\log N}}{\log N} = c_1\sqrt{\frac{B}{\log N}}.$$

Hence

$$\inf_{\widetilde{Q}} \sup_{Q} E\{W_1(Q,\widetilde{Q})\} \geq \frac{3c_1}{10} \sqrt{\frac{B}{\log N}} \geq \frac{3}{40e^4 \sqrt{c_0}} \sqrt{\frac{B}{\log N}}.$$

This completes the proof.

A Auxiliary proofs

Lemma A.1. Suppose Q is a distribution on [0, B] and $\{X_i, i \in [N]\}$ are N observations generated from h_Q defined in (6.1). For an arbitrary $\delta \in (0, 1)$, the following inequality

$$\left| \sum_{x=0}^{\infty} b_x \left(h_Q^{obs}(x) - h_Q(x) \right) \right| \le \max_x |b_x| \sqrt{\frac{\log(2/\delta)}{2N}},$$

holds with probability at least $1 - \delta$, where $b_x \in \mathbb{R}$ and $h_Q^{obs} = \sum_{i=1}^N I(x = X_i)/N$.

Proof of Lemma A.1. By noting that $E\{h_Q^{obs}(x)\}=h_Q(x)$, this proof is basically an application of McDiarmid's inequality.

Let $\phi : \mathbb{R}^N \to \mathbb{R}$ be a function of $(y_1, \dots, y_N) \in \mathbb{R}^N$ such that

$$\phi(y_1, \dots, y_N) := \frac{1}{N} \sum_{i=1}^{N} \sum_{x=0}^{\infty} b_x I(x \in \{y_i\}).$$

Since for any $y_1, \ldots, y_N, y_{i'} \in \mathbb{R}$

$$|\phi(y_1, \dots, y_i, \dots, y_N) - \phi(y_1, \dots, y_{i'}, \dots, y_N)| \le \max_{x>0} |b_x| \frac{1}{N},$$

it follows from McDiarmid's inequality that for all $\epsilon > 0$

$$P(|\phi(X_1,...,X_N) - E\{\phi(X_1,...,X_N)\}| \ge \epsilon) \le 2 \exp\left(\frac{-2N\epsilon^2}{\max_{x>0} |b_x|^2}\right),$$

or equivalently,

$$P(|\sum_{x=0}^{\infty} b_x \left(h_x^{obs} - h_Q(x) \right)| \ge \epsilon) \le 2 \exp\left(\frac{-2N\epsilon^2}{\max_{x \ge 0} |b_x|^2} \right)$$

by noting that

$$\phi(X_1, \dots, X_N) - E\{\phi(X_1, \dots, X_N)\} = \sum_{x=0}^{\infty} b_x \left(h_x^{obs} - h_Q(x)\right).$$

Hence for an arbitrary $\delta \in (0,1)$ the following inequality

$$\left| \sum_{x=0}^{\infty} b_x \left(h_Q^{obs}(x) - h_Q(x) \right) \right| \le \max_x |b_x| \sqrt{\frac{\log(2/\delta)}{2N}}$$

holds with probability at least $1 - \delta$.

Lemma A.2. Suppose Q is a distribution on [0, B] and $\{X_i, i \in [N]\}$ is a random sample from h_Q defined in (6.1). \widehat{Q} defined in (6.2) is a NPMLE of the mixing distribution Q. For an arbitrary $\delta \in (0,1)$ and an arbitrary $\epsilon \in (0,1)$, there exist constants $N(\epsilon) > 0$ and $C = C(\epsilon) > 0$ such that for all $N \geq N(\epsilon)$,

$$\left| \sum_{x=0}^{\infty} b_x \left(h_Q^{obs}(x) - h_{\widehat{Q}}(x) \right) \right| \leq C \max_{x \geq 0} |b_x| \sqrt{\frac{B \vee 1}{N^{1 - \epsilon} \delta^{1 + \epsilon}}}$$

holds with probability at least $1 - \delta$.

Proof of Lemma A.2. Let $\mathbf{h}_Q^{obs} := \left(h_Q^{obs}(0), h_Q^{obs}(1), \ldots\right)^T$, $\mathbf{h}_{\widehat{Q}} := \left(h_{\widehat{Q}}(0), h_{\widehat{Q}}(1), \ldots\right)^T$ and $\mathbf{h}_Q := \left(h_Q(0), h_Q(1), \ldots\right)^T$. For simplicity, \mathbf{h}_Q^{obs} , $\mathbf{h}_{\widehat{Q}}$ and \mathbf{h}_Q also represent distributions with respect to corresponding probability mass functions $x \mapsto h_Q^{obs}(x)$, $x \mapsto h_{\widehat{Q}}(x)$ and $x \mapsto h_Q(x)$.

This proof consists of two steps. In the first step, we prove that $\left|\sum_{x=0}^{\infty} b_x \left(h_Q^{obs}(x) - h_{\widehat{Q}}(x)\right)\right|$ can be upper bounded by $\mathrm{KL}(\mathbf{h}_Q^{obs}, \mathbf{h}_Q)$, where KL is the Kullback–Leibler divergence. In the second step, we upper bound $\mathrm{KL}(\mathbf{h}_Q^{obs}, \mathbf{h}_Q)$ by truncation arguments.

Step 1. It follows from the triangle inequality that

$$\left| \sum_{x=0}^{\infty} b_x \left(h_Q^{obs}(x) - h_{\widehat{Q}}(x) \right) \right| \le \max_{x \ge 0} |b_x| \sum_{x=0}^{\infty} \left| h_Q^{obs}(x) - h_{\widehat{Q}}(x) \right| = \max_{x \ge 0} |b_x| ||\mathbf{h}_Q^{obs} - \mathbf{h}_{\widehat{Q}}||_1,$$

where $\|\mathbf{h}_{Q}^{obs} - \mathbf{h}_{\widehat{Q}}\|_{1}$ is the total variation distance between distributions \mathbf{h}_{Q}^{obs} and $\mathbf{h}_{\widehat{Q}}$. Then it follows from Pinsker's inequality (see Proposition A.1) that

$$\|\mathbf{h}_{Q}^{obs} - \mathbf{h}_{\widehat{Q}}\|_{1} \le \sqrt{\frac{1}{2} \cdot \text{KL}(\mathbf{h}_{Q}^{obs}, \mathbf{h}_{\widehat{Q}})},$$

where KL is the Kullback-Leibler divergence, and hence

$$\left| \sum_{x=0}^{\infty} b_x \left(h_Q^{obs}(x) - h_{\widehat{Q}}(x) \right) \right| \leq \max_{x \geq 0} |b_x| \sqrt{\frac{1}{2} \cdot \text{KL}(\mathbf{h}_Q^{obs}, \mathbf{h}_{\widehat{Q}})} \leq \max_{x \geq 0} |b_x| \sqrt{\frac{1}{2} \cdot \text{KL}(\mathbf{h}_Q^{obs}, \mathbf{h}_Q)},$$

by noting that maximum likelihood estimators maximize likelihood functions.

Proposition A.1. (Pinsker's Inequality, see Cover and Thomas (2006).) For discrete distributions P and Q, it follows that

$$KL(P,Q) \ge 2||P - Q||_1^2$$

where KL(P,Q) is the Kullback-Leibler divergence between P and Q, and $||P-Q||_1$ is the total variation distance between P and Q.

Step 2. Let $\{T_i := X_i I(X_i \leq \lfloor 2B \rfloor) + (\lfloor 2B \rfloor + 1) I(X_i \geq \lfloor 2B \rfloor + 1), i \in [N]\}$ be a truncated sample of $\{X_i, i \in [N]\}$, where $\lfloor 2B \rfloor$ denotes the larger integer that is less or equal to 2B. Let t_Q be the probability mass function of T_1 and let t_Q^{obs} be the sample version of t_Q , i.e. for $x = 0, \ldots, \lfloor 2B \rfloor + 1$

$$x \mapsto t_Q(x) := P(T_1 = x)$$
 and $x \mapsto t_Q^{obs}(x) := \frac{1}{N} \sum_{i=1}^N I(T_i = x).$

Note that $t_Q(x) = h_Q(x)$, $t_Q^{obs}(x) = h_Q^{obs}(x)$ for $x = 0, ..., \lfloor 2B \rfloor$ and $t_Q(\lfloor 2B \rfloor + 1) = \sum_{x \geq \lfloor 2B \rfloor + 1} h_Q(x)$, $t_Q^{obs}(\lfloor 2B \rfloor + 1) = \sum_{x \geq \lfloor 2B \rfloor + 1} h_Q^{obs}(x)$ and hence

$$\begin{aligned} \mathrm{KL}(\mathbf{h}_{Q}^{obs}, \mathbf{h}_{Q}) &= \sum_{x \geq 0} h_{Q}^{obs}(x) \log \frac{h_{Q}^{obs}(x)}{h_{Q}(x)} \\ &= \mathrm{KL}(\mathbf{t}_{Q}^{obs}, \mathbf{t}_{Q}) - t_{Q}^{obs}(\lfloor 2B \rfloor + 1) \log \frac{t_{Q}^{obs}(\lfloor 2B \rfloor + 1)}{t_{Q}(\lfloor 2B \rfloor + 1)} + \sum_{x \geq \lfloor 2B \rfloor + 1} h_{Q}^{obs}(x) \log \frac{h_{Q}^{obs}(x)}{h_{Q}(x)}, \end{aligned}$$

where $\mathbf{t}_Q^{obs} := (t_Q^{obs}(0), \dots, t_Q^{obs}(\lfloor 2B \rfloor + 1))$ and $\mathbf{t}_Q := (t_Q(0), \dots, t_Q(\lfloor 2B \rfloor + 1))$ are also viewed as

distributions with respect to corresponding probability mass functions $x \mapsto t_Q(x)$ and $x \mapsto t_Q^{obs}(x)$. If $t_Q^{obs}(\lfloor 2B \rfloor + 1) = 0$, then $t_Q^{obs}(\lfloor 2B \rfloor + 1) \log \frac{t_Q^{obs}(\lfloor 2B \rfloor + 1)}{t_Q(\lfloor 2B \rfloor + 1)} = 0$. If not, it follows from $\log(1 + x) \le x$ for x > 0 that

$$-t_Q^{obs}(\lfloor 2B \rfloor + 1) \log \frac{t_Q^{obs}(\lfloor 2B \rfloor + 1)}{t_Q(\lfloor 2B \rfloor + 1)} \le t_Q(\lfloor 2B \rfloor + 1) - t_Q^{obs}(\lfloor 2B \rfloor + 1) = \sum_{x > \lfloor 2B \rfloor + 1} (h_Q(x) - h_Q^{obs}(x)).$$

Analogously, it can be proved that

$$\sum_{x \ge \lfloor 2B \rfloor + 1} h_Q^{obs}(x) \log \frac{h_Q^{obs}(x)}{h_Q(x)} \le \sum_{x \ge \lfloor 2B \rfloor + 1} \frac{(h_Q^{obs}(x) - h_Q(x))^2}{h_Q(x)} + \sum_{x \ge \lfloor 2B \rfloor + 1} (h_Q^{obs}(x) - h_Q(x))$$

and hence

$$-t_Q^{obs}(\lfloor 2B \rfloor + 1) \log \frac{t_Q^{obs}(\lfloor 2B \rfloor + 1)}{t_Q(\lfloor 2B \rfloor + 1)} + \sum_{x \ge \lfloor 2B \rfloor + 1} h_Q^{obs}(x) \log \frac{h_Q^{obs}(x)}{h_Q(x)} \le \sum_{x \ge \lfloor 2B \rfloor + 1} \frac{(h_Q^{obs}(x) - h_Q(x))^2}{h_Q(x)},$$

where the last term can be upper bounded by an analog of proof of Proposition 3.1(i) in Lambert and Tierney (1984) in the following substep.

Step 2(a). In this substep, we upper bound $\sum_{x>|2B|+1} (h_Q^{obs}(x) - h_Q(x))^2/h_Q(x)$.

Fix a $\epsilon > 0$, choose a $\gamma > 0$ in $(1 - \epsilon, 1)$ and an $a = (\sqrt{33} - 1)/4 \approx 1.19 > 1$, where \approx means approximately equal to. Define $A := a^{(1-\gamma)/3}$. By Hölder's inequality,

$$\begin{split} & N^{1-\epsilon} \sum_{x \geq \lfloor 2B \rfloor + 1} \frac{(h_Q^{obs}(x) - h_Q(x))^2}{h_Q(x)} \\ = & N^{1-\epsilon} \sum_{x \geq \lfloor 2B \rfloor + 1} \frac{(h_Q^{obs}(x) - h_Q(x))^2}{h_Q(x)} A^{-x} A^x \\ \leq & N^{1-\epsilon} \left(\sum_{x \geq \lfloor 2B \rfloor + 1} \frac{(h_Q^{obs}(x) - h_Q(x))^2}{h_Q(x)} A^{-x/\gamma} \right)^{\gamma} \left(\sum_{x \geq \lfloor 2B \rfloor + 1} \frac{(h_Q^{obs}(x) - h_Q(x))^2}{h_Q(x)} A^{x/(1-\gamma)} \right)^{1-\gamma}. \end{split}$$

Since A > 1, it follows that

$$N \cdot E \left\{ \sum_{x \ge \lfloor 2B \rfloor + 1} \frac{(h_Q^{obs}(x) - h_Q(x))^2}{h_Q(x)} A^{-x/\gamma} \right\} \le \sum_{x \ge \lfloor 2B \rfloor + 1} A^{-x/\gamma} = \frac{A^{-(\lfloor 2B \rfloor + 1)/\gamma}}{1 - A^{-1/\gamma}} \le \frac{A^{-1/\gamma}}{1 - A^{-1/\gamma}} < \infty$$

and hence for an arbitrary $\delta \in (0,1)$, the following inequality

$$N \sum_{x \ge |2B|+1} \frac{(h_Q^{obs}(x) - h_Q(x))^2}{h_Q(x)} A^{-x/\gamma} \le \frac{A^{-1/\gamma}}{1 - A^{-1/\gamma}} \frac{1}{\delta}$$

holds with probability at least $1 - \delta$. Therefore, with probability at least $1 - \delta$, it follows that

$$\left(\sum_{x \ge \lfloor 2B \rfloor + 1} \frac{(h_Q^{obs}(x) - h_Q(x))^2}{h_Q(x)} A^{-x/\gamma}\right)^{\gamma} \le \left(\frac{A^{-1/\gamma}}{1 - A^{-1/\gamma}} \frac{1}{N\delta}\right)^{\gamma} \le \frac{1}{\left(A^{1/\gamma} - 1\right)^{\gamma}} \frac{1}{(N\delta)^{\gamma}}.$$

On the other hand, it follows from straight-forward algebra that

$$\sum_{x \ge \lfloor 2B \rfloor + 1} \frac{(h_Q^{obs}(x) - h_Q(x))^2}{h_Q(x)} A^{x/(1 - \gamma)} \le \sum_{x \ge \lfloor 2B \rfloor + 1} \frac{(h_Q^{obs}(x))^2}{h_Q(x)} a^{x/3} + \sum_{x \ge \lfloor 2B \rfloor + 1} h_Q(x) a^{x/3}.$$

The second term on the right is bounded by 1 by the following arguments. Since Q is supported on [0, B], it follows that for any fixed $x \ge 2B$, $\lambda \mapsto f(x|\lambda) := e^{-\lambda} \lambda^x / x!$ is a monotonically increasing function and hence

$$h_Q(x) = \int_0^B f(x|\lambda)dQ \le \sup_{\lambda \in [0,B]} f(x|\lambda) = f(x|B) = e^{-B}B^x/x!.$$

Therefore,

$$\sum_{x \ge |2B|+1} h_Q(x)a^x \le \sum_{x \ge 2B} e^{-B} \frac{B^x}{x!} a^x = e^{aB-B} \sum_{x \ge 2B} e^{-aB} \frac{(aB)^x}{x!} = e^{aB-B} P(\text{Poi}(aB) \ge 2B),$$

where Poi(aB) denotes a random variable following from Poisson distribution with a parameter aB. Moreover, it follows from Lemma A.5 that

$$P(\text{Poi}(aB) \ge 2B) \le \exp(-\{(2-a)/a\}^2 aB/3)$$

and hence

$$\sum_{x \ge |2B|+1} h_Q(x)a^x \le e^{aB-B} \exp\left(-\{(2-a)/a\}^2 aB/3\right) = \exp\{B(2a^2 + a - 4)/(3a)\} = 1$$

by verifying $2a^2 + a - 4 = 0$.

For any fixed k > 0, define A_N to be the event $\{h_Q^{obs}(x) > kh_Q(x)a^{x/3} \text{ for some } x \ge \lfloor 2B \rfloor + 1\}$. Then, by Markov's inequality

$$P(A_N) \le \sum_{x \ge |2B|+1} P(h_Q^{obs}(x) > kh_Q(x)a^{x/3}) \le \sum_{x \ge |2B|+1} \frac{E\{h_Q^{obs}(x)\}}{kh_Q(x)a^{x/3}} \le \frac{1}{k(a^{1/3} - 1)}.$$

Thus, $P(A_N)$ can be made arbitrarily small by choosing k large enough and on the complement of A_N we have

$$\sum_{x \ge |2B|+1} \frac{(h_Q^{obs}(x))^2}{h_Q(x)} a^{x/3} \le k^2 \sum_{x \ge |2B|+1} h_Q(x) a^x = k^2.$$

Therefore, for an arbitrary $\delta \in (0,1)$, with probability at least $1-\delta$, the following inequality

$$\sum_{x \ge \lfloor 2B \rfloor + 1} \frac{(h_Q^{obs}(x))^2}{h_Q(x)} a^{x/3} \le \left(\frac{1}{\delta} \frac{1}{a^{1/3} - 1}\right)^2$$

holds. Thus, for an arbitrary $\delta \in (0,1)$, with probability at least $1-\delta$, it follows that

$$\left(\sum_{x \ge \lfloor 2B \rfloor + 1} \frac{(h_Q^{obs}(x) - h_Q(x))^2}{h_Q(x)} A^{x/(1-\gamma)}\right)^{1-\gamma} \le \left(\left(\frac{1}{\delta} \frac{1}{a^{1/3} - 1}\right)^2 + 1\right)^{1-\gamma} \le \left(\frac{20}{\delta}\right)^{2-2\gamma},$$

where the last inequality follows from $a = (\sqrt{33} - 1)/4$ and $\gamma < 1$. For an arbitrary $\delta \in (0, 1/2)$,

with probability at least $1-2\delta$, it follows that

$$N^{1-\epsilon} \sum_{x \geq \lfloor 2B \rfloor + 1} \frac{(h_Q^{obs}(x) - h_Q(x))^2}{h_Q(x)} \leq N^{1-\epsilon} \frac{1}{\left(a^{\frac{1-\gamma}{3\gamma}} - 1\right)^{\gamma}} \frac{1}{(N\delta)^{\gamma}} \left(\frac{20}{\delta}\right)^{2-2\gamma} = N^{1-\epsilon-\gamma} \frac{20^{2-2\gamma}}{\left(a^{\frac{1-\gamma}{3\gamma}} - 1\right)^{\gamma}} \frac{1}{\delta^{2-\gamma}}$$

and hence by letting γ go to $1 - \epsilon$, it follows that

$$\sum_{x \ge \lfloor 2B \rfloor + 1} \frac{(h_Q^{obs}(x) - h_Q(x))^2}{h_Q(x)} \le \frac{20^{2\epsilon}}{(a^{\frac{\epsilon}{3(1 - \epsilon)}} - 1)^{1 - \epsilon}} \frac{1}{N^{1 - \epsilon}} \frac{1}{\delta^{1 + \epsilon}}.$$

Step 2(b). In this subset, we complete the upper bound of $KL(\mathbf{h}^{obs}, \mathbf{h}_Q)$.

As a result of Step 2(a), for arbitrary $\delta \in (0, 1/2)$ and $\epsilon \in (0, 1)$, with probability at least $1 - 2\delta$, it follows that

$$\mathrm{KL}(\mathbf{h}^{obs}, \mathbf{h}_Q) \le \mathrm{KL}(\mathbf{t}_Q^{obs}, \mathbf{t}_Q) + \frac{20^{2\epsilon}}{(a^{\frac{\epsilon}{3(1-\epsilon)}} - 1)^{1-\epsilon}} \frac{1}{N^{1-\epsilon}} \frac{1}{\delta^{1+\epsilon}}.$$

To upper bound $\mathrm{KL}(\mathbf{t}_Q^{obs}, \mathbf{t}_Q)$, the KL divergence between empirical observations and the true distribution for discrete distributions, it follows from Mardia et al. (2019) that with probability $1-\delta$

$$\mathrm{KL}(\mathbf{t}^{obs}, \mathbf{t}_Q) \leq \frac{2B+1}{2N} \log \frac{4N}{2B+1} + \frac{1}{N} \log \frac{3e}{\delta}$$

and hence for any $\epsilon \in (0,1)$ and $\delta \in (0,1/3)$, with probability at least $1-3\delta$ it follows that

$$KL(\mathbf{h}_{Q}^{obs}, \mathbf{h}_{Q}) \leq \frac{2B+1}{2N} \log \frac{4N}{2B+1} + \frac{1}{N} \log \frac{3e}{\delta} + \frac{20^{2\epsilon}}{(a^{\frac{\epsilon}{3(1-\epsilon)}} - 1)^{1-\epsilon}} \frac{1}{N^{1-\epsilon}} \frac{1}{\delta^{1+\epsilon}}.$$

Therefore, there exist positive constants $N_1 = N_1(\epsilon)$ and $C_1 = C_1(\epsilon)$ such that for $N \geq N_1$

$$\mathrm{KL}(\mathbf{h}_Q^{obs}, \mathbf{h}_Q) \le C_1 \frac{B \vee 1}{N^{1 - \epsilon} \delta^{1 + \epsilon}}$$

holds with probability at least $1-3\delta$ for any $\epsilon \in (0,1)$ and $\delta \in (0,1/3)$.

Proposition A.2.

(a) For any positive integer $k \geq 4(B \vee 1)$ and any 1-Lipschitz function $\lambda \mapsto \ell(\lambda)$ on [0,B] with $\ell(0) = 0$, there exists an approximation $\widehat{\ell}(\lambda) = \sum_{x=0}^k b_x \frac{\lambda^x e^{-\lambda}}{x!}$ such that

$$\sup_{\lambda \in [0,B]} |\widehat{\ell}(\lambda) - \ell(\lambda)| \le CB/k$$

and $\max_{x} |b_{x}| \leq C (\sqrt{ek}/B)^{k}$, where C > 1 is a universal constant.

(b) Suppose B > 0, $N \in \mathbb{N}^+$ and there exists constants $c_0, C_0 > 0$ such that $B \in [c_0 \log N, C_0 N]$. Then, for any fixed $c_0 \ge 100$ and any small $\epsilon \in (0, 0.02)$ there exist constants $C(\epsilon) > 0$ and $N(\epsilon) > 1$ and a sequence of coefficients $\{b_x\}_{x=0}^{\infty}$ such that for $N \ge N(\epsilon)$ any 1-Lipschitz function $\ell(\lambda)$ on [0, B] with $\ell(0) = 0$ can be approximated by $\widehat{\ell}(\lambda) = \sum_{x=0}^{\infty} b_x \frac{\lambda^x e^{-\lambda}}{x!}$ with an uniform approximation error of $C(\epsilon) \sqrt{\frac{B}{\log N}}$ with $\max_x |b_x| \le C(\epsilon) BN^{\epsilon}$.

Proof of Proposition A.2 (a). The following two facts are used in our proof.

Fact A.1 (Chapter 2.6 Equation 9 in Timan (2014)). Suppose k is a non-negative integer and $\lambda \mapsto p_k(\lambda)$ is a polynomial function with coefficients c_0, \ldots, c_k , i.e. $p_k(\lambda) := \sum_{x=0}^k c_x \lambda^x$. Then it follows that coefficients $\{c_x\}_{x=0}^k$ satisfy

$$|c_x| \le \frac{k^x}{x!} \max_{|\lambda| \le 1} |p_k(\lambda)|.$$

Fact A.2 (Approximating e^{λ} with Taylor expansion). Let $\lambda \in [0, B]$. For any $k \geq 2B$, it follows that

$$e^{\lambda} - \sum_{x=0}^{k} \frac{\lambda^x}{x!} = \sum_{x=k+1}^{\infty} \frac{\lambda^x}{x!} = \frac{\lambda^k}{k!} \sum_{x=1}^{\infty} \left(\frac{\lambda}{k+x} \cdots \frac{\lambda}{k+1} \right) \le \frac{\lambda^k}{k!} \sum_{x=1}^{\infty} \frac{1}{2^x} = \frac{\lambda^k}{k!}$$

and hence

$$|e^{\lambda} - \sum_{x=0}^{k} \frac{\lambda^x}{x!}|/e^{\lambda} \le \frac{\lambda^k}{k!e^{\lambda}} \le \frac{B^k}{k!e^B}.$$

Applying Fact A.2, it holds that for any $k \geq 2B$, there exists a polynomial $q_k(\lambda) = \sum_{x=0}^k \lambda^x/x!$ of degree k such that $|1 - q_k(\lambda)e^{-\lambda}| \leq B^k/(k!e^B)$ for all $\lambda \in [0, B]$. It is well known through Jackson's theorem (see Lemma A.3) that for any 1-Lipschitz function $\ell(\cdot)$ on [0, B], there exists a polynomial $p_k(\lambda)$ of degree k such that $\sup_{\lambda \in [-B,B]} |\ell(\lambda) - p_k(\lambda)| \leq C_1 B/k$, where $\ell(\lambda) := -\ell(-\lambda)$ for $\lambda < 0$ and $C_1 > 0$ is a universal constant independent of k and ℓ . Combining $p_k(\lambda)$, $q_k(\lambda)$ and the fact that $|p_k(\lambda)| \leq B + C_1 B/k \leq (1 + C_1)B$, it follows that for $\lambda \in [0, B]$

$$|p_k(\lambda)q_k(\lambda)e^{-\lambda} - \ell(\lambda)| \le |p_k(\lambda)(q_k(\lambda)e^{-\lambda} - 1)| + |p_k(\lambda) - \ell(\lambda)| \le (1 + C_1)\frac{B}{k} \left(\frac{kB^k e^k}{\sqrt{kk^k e^B}} + 1\right),$$

where the last inequality follows from $k! \geq \sqrt{k} (k/e)^k$ for $k \geq 2$ by Stirling's approximation. It further follows from the increasing monotonicity of $B \mapsto B^k/e^B$ for $B \leq k/2$ that

$$\sqrt{k}B^k e^k/(k^k e^B) \le \sqrt{k}(k/2)^k e^k/(k^k e^{k/2}) = \sqrt{k}(\sqrt{e}/2)^k < 1,$$

where the last inequality holds for all $k \geq 2$, and hence

$$|p_k(\lambda)q_k(\lambda)e^{-\lambda} - \ell(\lambda)| \le 2(1+C_1)B/k$$

for $k \geq 2(B \vee 1)$. Therefore, we have shown that for any $k \geq 2(B \vee 1)$, there exists a function

$$\widehat{\ell}(\lambda) = p_k(\lambda)q_k(\lambda)e^{-\lambda} = \sum_{x=0}^{2k} b_x \frac{\lambda^x e^{-\lambda}}{x!}$$

such that $|\hat{\ell}(\lambda) - \ell(\lambda)| \leq 2(1 + C_1)B/k$. For the bounded on the coefficients b_x , first let us define the polynomial $r(\lambda) := p_k(B \cdot \lambda)q_k(B \cdot \lambda) = \sum_{x=0}^{2k} b_x' \frac{\lambda^x}{x!}$. Note that $b_x = b_x'/B^x$,

$$|r(\lambda)| \le (B + 2(1 + C_1)B/k)e^B \le 2(1 + C_1)Be^B$$

for $\lambda \in [0,1]$ and

$$|r(\lambda)| \le |q_k(B \cdot \lambda)|(1 + C_1)B \le \left(1 + \frac{B^{k+1}}{(k+1)!}\right)(1 + C_1)B \le \left(1 + e/2e^B\right)(1 + C_1)B \le 3(1 + C_1)Be^B$$

for $\lambda \in [-1,0)$. Then we can apply Fact A.1 for the polynomial $r(\lambda)$, which implies that

$$\frac{|b_x'|}{x!} \le \frac{(2k)^x}{x!} \max_{|\lambda| < 1} |r(\lambda)| \le \frac{(2k)^x}{x!} 3(1 + C_1) B e^B,$$

and hence

$$\max_{x} |b_x| = \max_{x} \frac{|b_x'|}{B^x} \le \max_{x} \left(\frac{2k}{B}\right)^x 3(1+C_1)Be^B = 3(1+C_1)\left(\frac{2k}{B}\right)^{2k} Be^B \le 3(1+C_1)\left(\frac{2\sqrt{ek}}{B}\right)^{2k},$$
 where the last inequality follows from $B \le k/2 \le \exp(k/2)$ and $e^B \le \exp(k/2)$.

Proof of Proposition A.2 (b). Since $B \ge c_0 \log N$, we have $B \ge 1$ for sufficiently large N. Note that $\lambda \mapsto \frac{1}{B}\ell(B\lambda)$ is a Lipschitz-1 function on [0,1]. By Proposition A.4, it follows that there exists a sequence of coefficients $\{b_x\}_{x=0}^{\infty}$ such that

$$\left| \frac{1}{B} \ell(B\lambda) - \sum_{x=0}^{\infty} b_x P(\operatorname{Poi}(B\lambda) = x) \right| \le C(\epsilon) \sqrt{\frac{1}{B \log N}}, \text{ for any } \lambda \in [0, 1],$$

where $b_x = 0$ for x > 4B, and

$$\left| b_x - \frac{1}{B} \ell \left(B \cdot \frac{x}{B} \right) \right| \le \frac{C(\epsilon)(1 + x^{1/2})N^{\epsilon}}{B}, \text{ for } x \le 4B.$$

Defining $b_x^* = Bb_x$ and replacing $B\lambda$ by λ , it follows that

$$|\ell(\lambda) - \sum_{x=0}^{\infty} b_x^* P(\operatorname{Poi}(\lambda) = x)| \le C(\epsilon) \sqrt{\frac{B}{\log N}}, \text{ for any } \lambda \in [0, B],$$

where $b_x^* = 0$ for x > 4B, and

$$|b_x^* - \ell(x)| \le C(\epsilon)(1 + x^{1/2})N^{\epsilon}$$
, for $x \le 4B$.

Moreover, It follows from the triangle inequality that $|b_x^*| \leq 4B + C(\epsilon)(1 + 2B^{1/2})N^{\epsilon} = O(BN^{\epsilon})$.

The following proposition is an extension of Wu and Yang (2016, Lemma 3); see also Wu and Yang (2020b, Section 3.3) for a nice survey.

Proposition A.3 (Lemma 32 in Jiao et al. (2018)). Suppose U_0 , U_1 are two random variables supported on [a-M,a+M], where $a \ge M \ge 0$ are constants. Suppose $E\{U_0^j\} = E\{U_1^j\}, 0 \le j \le L$. Denote the marginal distribution of X where $X|\lambda \sim Poi(\lambda)$, $\lambda \sim U_i$ as F_i , where i = 0,1. If $L+1 \ge (2eM)^2/a$, then $TV(F_0,F_1) \le 2(eM/\sqrt{a(L+1)})^{L+1}$

Proposition A.4. Suppose B > 0 and $N \in \mathbb{N}^+$ and there exists constants $c_0, C_0 > 0$ such that $B \in [c_0 \log N, C_0 N]$. Let $\ell(\cdot)$ be any Lipschitz-1 function on \mathbb{R} with $\ell(0) = 0$. Then, for any fixed $c_0 \geq 96$ and any small $\epsilon \in (0, 0.02)$ there exist positive constants $C(\epsilon) > 0$ and $N(\epsilon) > 1$ depending on ϵ and a sequence of coefficients $\{b_x\}_{x=0}^{\infty}$ such that the following inequality holds for $N \geq N(\epsilon)$, i.e.

$$|\ell(\lambda) - \sum_{x=0}^{\infty} b_x P(Poi(B\lambda) = x)| \le C(\epsilon) \sqrt{\frac{1}{B \log N}}, \lambda \in [0, 1]$$
(A.1)

where $b_x = 0$ for x > 4B, and

$$\left| b_x - \ell\left(\frac{x}{B}\right) \right| \le C(\epsilon)(1 + x^{1/2})\frac{N^{\epsilon}}{B}, \text{ for any } x \le 4B.$$
 (A.2)

Proof of Proposition A.4. Note that Proposition A.4 is an analogue of Theorem 5 in Han and Shiragur (2020) and these lemmas below will be used in the following proof.

Lemma A.3 (Jackson's theorem, Lemma 10 of Han and Shiragur (2020)). Let k > 0 be any integer, and $[a,b] \subseteq \mathbb{R}$ be any bounded interval. For any Lipschitz-1 function $\ell(\cdot)$ on [a,b], there exists a universal constant C independent of k,ℓ such that there exists a polynomial $p_k(\cdot)$ of degree at most k such that

$$|\ell(\lambda) - p_k(\lambda)| \le C\sqrt{(b-a)(\lambda-a)}/k, \ \forall \lambda \in [a,b].$$
 (A.3)

In particular, the following norm bound holds:

$$\sup_{\lambda \in [a,b]} |\ell(\lambda) - p_k(\lambda)| \le C(b-a)/k. \tag{A.4}$$

Lemma A.4 (Lemma 11 of Han and Shiragur (2020)). Let $p_k(\lambda) = \sum_{x=0}^k a_x \lambda^x$ be a polynomial of degree at most k such that $|p_k(\lambda)| \leq A$ for $\lambda \in [a, b]$. Then

1. If $a + b \neq 0$, then

$$|a_x| \le 2^{7k/2} A \left| \frac{a+b}{2} \right|^{-x} \left(\left| \frac{b+a}{b-a} \right|^k + 1 \right), \quad x = 0, \dots, k.$$

2. If a + b = 0, then $|a_x| \le Ab^{-x}(\sqrt{2} + 1)^k$, $x = 0, \dots, k$.

Lemma A.5 (Poisson tail inequality, Lemma 12 of Han and Shiragur (2020)). For $X \sim Poi(\lambda)$ and any $\delta > 0$, we have

$$P(X \ge (1+\delta)\lambda) \le \exp\left(-(\delta^2 \wedge \delta)\lambda/3\right)$$
 and $P(X \le (1-\delta)\lambda) \le \exp\left(-\delta^2 \lambda/3\right)$.

Lemma A.6 (Lemma 15 of Han and Shiragur (2020)). Define

$$g_{d,x}(z) := \sum_{d'=0}^{d} \binom{d}{d'} (-x)^{d-d'} \prod_{d''=0}^{d'-1} \left(z - \frac{2d''}{n} \right)$$

with $d \in \mathbb{N}, x \in [0, 1]$. Then for any $z \in [0, 1]$ and $d \ge 1$, the following identity holds:

$$g_{d,x}\left(z+\frac{2}{n}\right) - g_{d,x}(z) = \frac{2d}{n}g_{d-1,x}(z).$$

 $\textit{Moreover, if } nz/2 \in \mathbb{N} \textit{ and } \max\{|z-x|, 8d/n, \sqrt{8zd/n}\} \leq \Delta, \textit{ then } |g_{d,x}(z)| \leq (2\Delta)^d.$

Now we start our proof. Since $B \ge c_0 \log N$, we have $B \ge 1$ for sufficiently large N. Note that the proof here is an analog of proof of Theorem 5 in Han and Shiragur (2020), but has much more details. We could omit the following proof, but for the completeness of this paper, we decide to write it down.

We shall construct the following local intervals: for $c_1 := c_0/4$ and $m = 1, 2, \dots, M := \sqrt{B/(c_1 \log N)}$, define

$$I_m := \left[\frac{c_1 \log N}{B} \cdot (m-1)^2, \frac{c_1 \log N}{B} \cdot m^2 \right], \quad I'_m := \left[\frac{c_1 \log N}{B} \cdot (m-4/3)_+^2, \frac{c_1 \log N}{B} \cdot (m+1/3)^2 \right],$$

$$I''_m := \left[\frac{c_1 \log N}{B} \cdot (m-2)_+^2, \frac{c_1 \log N}{B} \cdot (m+1)^2 \right],$$

and without loss of generality we assume that M is an integer. Note that $M \geq 2$. We shall also define

$$\lambda_m := \frac{c_1 \log N}{B} \cdot \frac{(m - 4/3)_+^2 + (m + 1/3)^2}{2}$$

to be the center of I'_m . Note that $I_m \subset I'_m \subset I''_m$, and it follows from Lemma A.5 that for $m \geq 2$,

$$P(\text{Poi}(B\lambda) \notin BI'_m | \lambda \in I_m) \le 2N^{-c_1/27}.$$
 (A.5)

For m=1, it can be analogous to verify that the last display holds for m=1 and hence it holds for $m=1,\ldots,M$. Analogously, we have the following inequalities: for $m=1,\ldots,M$

$$P(\text{Poi}(B\lambda) \notin BI_m'' | \lambda \in I_m') \le 2N^{-c_1/3}$$
 (A.6)

and

$$P(\text{Poi}(B\lambda) \notin BI_m | \lambda \in I_m - I'_{m-1} - I'_{m+1}) \le 2N^{-c_1/12}.$$
 (A.7)

Now we use the local Poisson polynomial on each local interval I'_m constructed in Lemma A.7 to prove Proposition A.4.

We assume that $\sum_{x=0}^{\infty} b_x^{(m)} P(\text{Poi}(B\lambda/2) = x)$ is the Poisson polynomial given by Lemma A.7 on the *m*-th local interval I_m' , with *B* replaced by B/2. Now consider the following Poisson polynomial:

$$p(\lambda) := \sum_{x=0}^{\infty} b_x P(\text{Poi}(B\lambda) = x) \text{ with } b_x := \frac{1}{2^x} \sum_{m=1}^M \sum_{k \in BI_m/2} {x \choose k} b_{x-k}^{(m)}.$$
 (A.8)

We claim that the above polynomial with coefficients in (A.8) satisfies Proposition A.4. We first verify the inequality (A.1). Using a change of variable j = x - k, we have

$$p(\lambda) = \sum_{m=1}^{M} P(\operatorname{Poi}(B\lambda/2) \in BI_m/2) \sum_{j=0}^{\infty} b_j^{(m)} P(\operatorname{Poi}(B\lambda/2) = j).$$

Since I_m constitutes a partition of [0,1], for $\lambda \in [0,1]$ there exists $m^* = 1, 2, \dots, M$, such that $\lambda \in I_{m^*}$. We distinguish into three cases:

• Case 1: $\lambda \in I_{m^*} - I'_{m^*-1} - I'_{m^*+1}$. By (A.7), we have $P(\text{Poi}(B\lambda/2) \notin BI_{m^*}/2) \leq 2N^{-1}$ since $c_1 = c_0/4 \geq 24$, and therefore $P(\text{Poi}(B\lambda/2) \in BI_m/2) \leq 2N^{-2}$ for any $m \neq m^*$. Hence,

$$|\ell(\lambda) - p(\lambda)| \le C(\epsilon) \sqrt{\frac{\lambda}{B \log N}} + 4N^{-2} (1 + 2C(\epsilon)N^{\epsilon})$$

where we have used (A.10) in the second last inequality. As a result, the desired approximation error in (A.1) holds.

• Case II: $\lambda \in I_{m^*} \cap I'_{m^*+1}$. In this case, Lemma A.5 gives $P(\text{Poi}(B\lambda/2) \in BI_m/2) \leq N^{-2}$ for any $m \notin \{m^*, m^* + 1\}$. Consequently,

$$|\ell(\lambda) - p(\lambda)| \leq P(\operatorname{Poi}(B\lambda/2) \in BI_{m^*}/2) \left| \ell(\lambda) - \sum_{j=0}^{\infty} b_j^{(m^*)} P(\operatorname{Poi}(B\lambda/2) = j) \right|$$

$$+ P(\operatorname{Poi}(B\lambda/2) \in BI_{m^*+1}/2) \left| \ell(\lambda) - \sum_{j=0}^{\infty} b_j^{(m^*+1)} P(\operatorname{Poi}(B\lambda/2) = j) \right|$$

$$+ \sum_{m \neq m^*, m^*+1} P(\operatorname{Poi}(B\lambda/2) \in BI_m/2) \left| \sum_{j=0}^{\infty} b_j^{(m)} P(\operatorname{Poi}(B\lambda/2) = j) \right|,$$

and using Lemma A.7 and the same concentration bounds gives (A.1).

• Case III: $\lambda \in I_{m^*} \cap I'_{m^*-1}$. This case is entirely symmetric to Case II.

Combining the above three cases, we arrive at the inequality (A.1).

Next we verify the coefficient bound (A.2). By Lemma A.7, it is clear from the definition that $b_x = 0$ whenever $x \notin \bigcup_{m=1}^M BI_m''$ and hence $b_x = 0$ for $x \ge 4B$. Fix any $x \ge 0$ such that $b_x \ne 0$, assume that $x \in BI_{m^*}''$ (if there are multiple choices of m^* , pick an arbitrary one). We claim that any other $m = 1, 2, \dots, M$ such that $|m - m^*| \ge 5$ do not contribute to b_x in the summation (A.8). In fact, if there is non-zero coefficient $b_{x-k}^{(m)}$ in (A.8), we must have

$$x \in BI'''_{m^*} = c_1 \log N \cdot \left[(m^* - 2)_+^2, (m^* + 1)^2 \right], \quad k \in BI_m/2 = \frac{c_1 \log N}{2} \cdot \left[(m - 1)^2, m^2 \right],$$

 $x - k \in BI'''_m/2 = \frac{c_1 \log N}{2} \cdot \left[(m - 2)_+^2, (m + 1)^2 \right].$

Summing up, we must have at least one of

$$(m^*-2)_+^2 \le \frac{(m-1)^2 + (m-2)_+^2}{2}, \quad (m^*+1)^2 \ge \frac{m^2 + (m+1)^2}{2},$$

will fail whenever $|m-m^*| \geq 5$. Hence, there exists constants C_1, C_2 such that

$$|b_x| \le \frac{1}{2^x} \sum_{m=1}^M \sum_{k \in BI_m/2} \binom{x}{k} |b_{x-k}^{(m)}| \le C_1 \max_{m:|m-m^*| \le 4} \max_{j \ge 0} |b_j^{(m)}| \le \frac{C_2 C(\epsilon) (1 + x^{1/2}) N^{\epsilon}}{B}$$

establishing (A.2).

Lemma A.7. Suppose B > 0 and $N \in \mathbb{N}^+$ and there exists constants $c_0, C_0 > 0$ such that $B \in [c_0 \log N, C_0 N]$. Let $\ell(\cdot)$ be any Lipschitz-1 function on \mathbb{R} with $\ell(0) = 0$. Then, for any fixed $c_0 \geq 16$ and any small $\epsilon \in (0, 0.02)$ there exist constants $C(\epsilon) > 0$ and $N(\epsilon) > 1$ depending on ϵ and a sequence of coefficients $\{b_x\}_{x=0}^{\infty}$ such that the following inequality holds for $N \geq N(\epsilon)$, i.e.

$$|\ell(\lambda) - \sum_{x=0}^{\infty} b_x P(Poi(B\lambda) = x)| \le C(\epsilon) \sqrt{\frac{\lambda}{B \log N}}, \text{ for any } \lambda \in I'_m,$$
(A.9)

where $b_x = 0$ for $x \notin BI''_m$, and

$$\left| b_x - \ell\left(\frac{x}{B}\right) \right| \le \frac{C(\epsilon)(1 + x^{1/2})N^{\epsilon}}{B}, \text{ for any } x \in BI_m'', \tag{A.10}$$

where I'_m and I''_m are defined in the proof of Proposition A.4.

Proof of Lemma A.7. Since $B \geq c_0 \log N$, we have $B \geq 1$ for sufficiently large N. Recall that $c_1 = c_0/4 \geq 4$. Let $D := c_2 \log N$ where $c_2 > 0$ is a small constant specified later and without loss of generality it is assumed that D is an integer. Throughout the proof we will use C_1, C_2, \cdots to denote positive constants independent of (B, c_1, c_2) . For m = 1 it follows from Lemma A.3 that there exist coefficients $\{a_{1,d}\}_{d=0}^{D}$ such that

$$|\ell(\lambda) - \sum_{d=0}^{D} a_{1,d} (\lambda - \lambda_1)^d| \le C_1 \frac{\sqrt{\frac{c_1 \log N}{B} \cdot (4/3)^2 \lambda}}{D} = \frac{4C_1}{3c_2} \sqrt{\frac{c_1 \lambda}{B \log N}}$$

for all $\lambda \in I_1'$. If $m \geq 2$, it follows from Lemma A.3 that there exist coefficients $\{a_{m,d}\}_{d=0}^D$ such that

$$|\ell(\lambda) - \sum_{d=0}^{D} a_{m,d} (\lambda - \lambda_m)^d| \le \frac{10C_1}{3c_2} \frac{c_1(m - \frac{1}{2})}{B} \le \frac{10C_1c_1}{c_2B} \left(m - \frac{4}{3}\right),$$

where the last inequality follows from $m \ge 2$. Then it follows from $m \le \frac{4}{3} + \sqrt{\frac{B\lambda}{c_1 \log N}}$ for all $\lambda \in I'_m$ that

$$|\ell(\lambda) - \sum_{d=0}^{D} a_{m,d} (\lambda - \lambda_m)^d| \le \frac{10C_1}{c_2} \sqrt{\frac{c_1 \lambda}{B \log N}}.$$

Combining the above cases, it follows that for m = 1, ..., M and $\lambda \in I'_m$

$$|\ell(\lambda) - \sum_{d=0}^{D} a_{m,d} (\lambda - \lambda_m)^d| \le 10C_1 \frac{\sqrt{c_1}}{c_2} \sqrt{\frac{\lambda}{B \log N}}.$$

As a sequence, it follows that for $\lambda \in I'_m$

$$|\ell(\lambda_m) - \sum_{d=0}^{D} a_{m,d} (\lambda - \lambda_m)^d| \le |\ell(\lambda) - \ell(\lambda_m)| + |\ell(\lambda) - \sum_{d=0}^{D} a_{m,d} (\lambda - \lambda_m)^d| \le \frac{5c_1 m \log N}{B} \left(\frac{2}{3} + \frac{4C_1}{c_2 \log N}\right).$$

Moreover, applying Lemma A.4 on the shifted interval $I'_m - \lambda_m$ gives that for $d = 1, 2, \dots, D$

$$|a_{m,d}| \le 9\left(\frac{2}{3} + \frac{4C_1}{c_2 \log N}\right) \left(\frac{5}{3} \frac{c_1 m \log N}{B}\right)^{1-d} N^{c_2}.$$

As for d=0, choosing $\lambda=\lambda_m$ in the above inequality gives $a_{m,0}\leq |\ell(\lambda_m)|+20C_1\frac{c_1m}{Bc_2}\leq 1+20C_1\frac{\sqrt{c_1}}{c_2}\sqrt{\frac{1}{B\log N}}$.

Next we write the above polynomial as a linear combination of Poisson polynomials. Since

$$\sum_{x=0}^{\infty} \frac{x!}{(x-d)!B^d} \cdot P(\operatorname{Poi}(B\lambda) = x) = \lambda^d$$

where $y! := \infty$ for y < 0, we have

$$\sum_{d=0}^{D} a_{m,d} (\lambda - \lambda_m)^d = \sum_{x=0}^{\infty} b_x^* P(\operatorname{Poi}(B\lambda) = x),$$

where $b_x^* := \sum_{d=0}^D a_{m,d} \sum_{d'=0}^d {d \choose d'} (-\lambda_m)^{d-d'} \frac{j!}{(x-d')!B^{d'}}$.

In other words, the inequality holds for the coefficients $\{b_x^*\}_{x=0}^{\infty}$. Now we define $\{b_x\}_{x=0}^{\infty}$ to be the truncated version of $\{b_x^*\}_{x=0}^{\infty}$:

$$b_x = b_x^* \cdot 1(x \in BI_m'').$$

Clearly $b_x=0$ for all $x\notin BI_m''$. By Lemma A.6, for $d=1,2,\cdots,D,$

$$\left| \sum_{d'=0}^{d} \binom{d}{d'} (-\lambda_{m})^{d-d'} \frac{x!}{(x-d')!B^{d'}} \right|$$

$$\leq \left\{ \begin{cases} \left(8 \max \left\{ \frac{c_{1}m \log N}{B}, \frac{1+c_{2} \log N}{B}, \frac{m\sqrt{(c_{1} \log N)(1+c_{2} \log N)}}{B} \right\} \right)^{d} & \text{if } x \in BI_{m}'' \\ \left(8 \max \left\{ \left| \frac{x}{B} - \lambda_{m} \right| / 4, \frac{1+c_{2} \log N}{B}, \frac{m\sqrt{(c_{1} \log N)(1+c_{2} \log N)}}{B} \right\} \right)^{d} & \text{otherwise.} \end{cases}$$

Suppose $c_2 < c_1$. Then for $N \ge \exp(1/c_2)$, it follows that $c_2 \log N \ge 1$ and hence

$$\frac{1+c_2\log N}{B} \leq \frac{2c_2\log N}{B} \leq \frac{2c_1m\log N}{B} \text{ and } \frac{m\sqrt{(c_1\log N)(1+c_2\log N)}}{B} \leq \frac{2c_1m\log N}{B}.$$

Therefore,

$$\left| \sum_{d'=0}^{d} {d \choose d'} (-\lambda_m)^{d-d'} \frac{x!}{(x-d')!B^{d'}} \right| \le \begin{cases} \left(16 \frac{c_1 m \log N}{B} \right)^d & \text{if } x \in BI_m'' \\ \left(8 \left| \frac{x}{B} - \lambda_m \right| \right)^d & \text{otherwise.} \end{cases}$$

Hence, for $x \in BI''_m$, we have

$$|b_x - a_{m,0}| = |b_x^* - a_{m,0}| \le \frac{17}{B} \left(\frac{2}{3} + \frac{4C_1}{c_2 \log N} \right) c_1 \log N \cdot \left(\sqrt{\frac{x}{c_1 \log N}} + 2 \right) N^{3c_2}.$$

Since $c_2 < c_1$ and $c_2 \log N \ge 1$, it follows that $c_1 \log N \ge 1$ and hence

$$|b_x - a_{m,0}| = |b_x^* - a_{m,0}| \le 34c_1 \left(\frac{2}{3} + 4C_1\right) \cdot \frac{(\sqrt{x} + 1)N^{4c_2}}{B},$$

for N sufficiently large (depending on c_2).

Moreover, for any $x \in BI''_m$

$$|a_{m,0} - \ell\left(\frac{x}{B}\right)| \le \left(8c_1 + 40C_1\frac{c_1}{c_2}\right) \frac{(\sqrt{x} + 1)\log N}{B}$$

and therefore a triangle inequality gives the inequality (A.10).

As for the other inequality (A.9), by triangle inequality it suffices to prove that

$$\sum_{x \notin BI_m''} |b_x^*| \cdot P(\text{Poi}(B\lambda) = x) = O(N^{-1}), \text{ for any } \lambda \in I_m'.$$

To prove the last display, first note that for $x \notin BI''_m$, we have

$$|x - B\lambda_m| \ge 2c_1 m \log N$$

and

$$|b_x^*| \le C(c_1, c_2) + 17\left(\frac{2}{3} + \frac{4C_1}{c_2 \log N}\right) N^{c_2} \left(\frac{7|x - B\lambda_m|}{\sqrt{c_1 B\lambda_m \log N}}\right)^D,$$

where $C(c_1, c_2)$ is a constant depending on c_1, c_2 . Futhermore, by the Chernoff bound (Lemma A.5), we have

$$P(\operatorname{Poi}(B\lambda) = x) \le \exp\left(-\frac{1}{3}|x - B\lambda| \left(\frac{|x - B\lambda|}{B\lambda} \wedge 1\right)\right).$$

Since for all $\lambda \in I_m'$ and $x \notin BI_m''$ we have $|x - B\lambda| \ge 4c_1m \log N$ and $B\lambda \le 4c_1m^2 \log N$, it follows that $|x - B\lambda|/(B\lambda) \ge 1/m$ and hence

$$P(\operatorname{Poi}(B\lambda) = x) \le \exp\left(-\frac{1}{6} \cdot c_1 \log N \cdot \frac{|x - B\lambda|}{\sqrt{c_1 B\lambda_m \log N}}\right).$$

Moreover, the assumption $x \notin BI_m''$ implies that $|x - B\lambda_m|/\sqrt{c_1B\lambda_m \log N} \ge 2 > 0$. Consequently, whenever $\lambda \in I_m'$ and $x \notin BI_m''$, we have

$$\sum_{x \notin BI_m''} |b_x^*| P(\text{Poi}(B\lambda) = x)$$

$$\leq 2C(c_1,c_2)N^{-c_1/3} + \sum_{x \notin BI'''} C_3 \exp\left(10c_2 \log N \cdot \log \frac{|x-B\lambda_m|}{\sqrt{c_1B\lambda_m \log N}} - \frac{1}{6} \cdot c_1 \log N \cdot \frac{|x-B\lambda|}{\sqrt{c_1B\lambda_m \log N}}\right),$$

where the first term in the last display follows from (A.6) and C_3 in the second term is a positive constant which doesn't depend on c_1 . Then by choosing $c_2 > 0$ small enough we arrive at an exponent= $\left(-\frac{1}{7}c_1\log N\frac{|x-B\lambda_m|}{\sqrt{c_1B\lambda_m\log N}}\right)$. It follows from $|x-B\lambda_m|/\sqrt{c_1B\lambda_m\log N} \ge 2 > 0$ that

$$\sum_{x \notin BI_m''} |b_x^*| P(\text{Poi}(B\lambda) = x) \le 2C(c_1, c_2) N^{-c_1/3} + C_3 N^{-2c_1/7} = O(N^{-2c_1/7}) = O(N^{-1}), \text{ for } c_1 \ge 4.$$

This completes the proof.

B Implementation details in Section 5

Let $n_1 = 13$ and $n_2 = 10$ denote the number of subjects in ASD and control groups respectively and n = 23 represent the number of total subjects. Since 99 percent of $\{X_{ij}^{(k)}/r_{ij}^{(k)}, i \in [N_{jk}], j \in [n_k], k \in [K]\}$ for 100 genes are smaller than 15.09, we choose B = 20. We use VEM to compute NPMLEs with a stop tolerance 0.01. The testings with covariance adjustments \hat{T}_Z and $\hat{T}_{h,Z}$ are conducted by R package "ideas" by Sun and Zhang with 10^5 Monte Carlo simulations.

To account for covariates, the pseudo-F statistics described in Section 2 has to be changed a little bit. Let \mathbf{D}_n be the n by n distance matrix corresponding to the mixing distributions, with each entry equal to the squared W_1 distance between the two corresponding NPMLEs, and let

$$\mathbf{G}_n := \left(\mathbf{I}_n - \frac{1}{n} \mathbf{1}_n \mathbf{1}_n^{\top}\right) \mathbf{A}_n \left(\mathbf{I}_n - \frac{1}{n} \mathbf{1}_n \mathbf{1}_n^{\top}\right),$$

be the Grower's center matrix of \mathbf{A}_n , where $\mathbf{A}_n := -(1/2)\mathbf{D}_n$, $\mathbf{1}_n := (\underbrace{1,1,\ldots,1}_n)^{\top}$, and \mathbf{I}_n stands for the *n*-dimensional identity matrix. Note that \mathbf{G}_n may have some negative eigenvalues, and we

set those negative eigenvalues to 0. Let \mathbf{Z} be an n by 5 matrix consisting of diagnostics (1 as ASD and 0 as control), age, sex, seqbatch, and RIN. Let \mathbf{H}_Z be the hat matrix $\mathbf{H}_Z := \mathbf{Z}(\mathbf{Z}^{\mathsf{T}}\mathbf{Z})^{-1}\mathbf{Z}^{\mathsf{T}}$. Then the new F-statistic accounting for covariates is

$$\widehat{F}_Z := \frac{\operatorname{tr}(\mathbf{H}_Z \mathbf{G} \mathbf{H}_Z)}{\operatorname{tr}((\mathbf{I} - \mathbf{H}_Z) \mathbf{G} (\mathbf{I} - \mathbf{H}_Z))},$$
(B.1)

where $\operatorname{tr}(\cdot)$ denotes the trace of a matrix. To implement the permutation test, we permute the variable "diagnostics" with all the rest covariates fixed and accordingly generate a new data matrix Z^{π} . The corresponding F-statistic is denoted by \widehat{F}_{Z}^{π} and the p-value is

the number of permutations
$$\pi$$
 such that $\widehat{F}_Z^{\pi} \ge \widehat{F}_Z$ the number of all possible permutations π . (B.2)

When replacing the distance matrix \mathbf{D}_n by the corresponding Poisson-smoothed version, the corresponding p-value is

the number of permutations
$$\pi$$
 such that $\widehat{F}_{h,Z}^{\pi} \ge \widehat{F}_{h,Z}$, the number of all possible permutations π (B.3)

where $\widehat{F}_{h,Z}$ and $\widehat{F}_{h,Z}^{\pi}$ are the Poisson-smoothed versions of \widehat{F}_{Z} and \widehat{F}_{Z}^{π} .

The above two testing procedures are abbreviated as \widehat{T}_Z and $\widehat{T}_{h,Z}$.

Acknowledgement

The authors would like to thank Yihong Wu for his very informative remarks on the issue of uniqueness of NPMLEs and concavity of the nonparametric Poisson likelihood functions. The authors would also like to thank Jiahua Chen, Matthew Stephens, and Jon Wellner for pointing out related literature and for helpful discussions.

References

Anderson, M. J. (2001). A new method for non-parametric multivariate analysis of variance. *Austral Ecology*, 26(1):32–46.

Baisch, B., Cai, S., Li, Z., and Pinheiro, V. (2017). Reaction time of children with and without autistic spectrum disorders. *Open Journal of Medical Psychology*, 6:166–178.

Benachenhou, S., Etcheverry, A., Galarneau, L., Dubé, J., and Çaku, A. (2019). Implication of hypocholesterolemia in autism spectrum disorder and its associated comorbidities: A retrospective case–control study. *Autism Research*, 12(12):1860–1869.

Berry, K. J. and Mielke, P. W. (1983). Moment approximations as an alternative to the F test in analysis of variance. *British Journal of Mathematical and Statistical Psychology*, 36(2):202–206.

Bi, Y. and Davuluri, R. V. (2013). NPEBseq: Nonparametric empirical bayesian-based procedure for differential expression analysis of RNA-seq data. *BMC Bioinformatics*, 14:262.

Billingsley, P. (1999). Convergence of Probability Measures. Wiley, 2nd edition.

- Böhning, D. (1982). Convergence of Simar's algorithm for finding the maximum likelihood estimate of a compound Poisson process. *Annals of Statistics*, 10(3):1006–1008.
- Böhning, D. (1985). Numerical estimation of a probability measure. *Journal of Statistical Planning and Inference*, 11(1):57–69.
- Böhning, D. (1986). A vertex-exchange-method in D-optimal design theory. Metrika, 33:337–347.
- Boik, R. J. (1987). The Fisher-Pitman permutation test: A non-robust alternative to the normal theory F test when variances are heterogeneous. *British Journal of Mathematical and Statistical Psychology*, 40(1):26–42.
- Calarge, C. A. and Schlechte, J. A. (2017). Bone mass in boys with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 47(6):1749–1755.
- Cameron, J. M., Levandovskiy, V., Roberts, W., Anagnostou, E., Scherer, S., Loh, A., and Schulze, A. (2017). Variability of creatine metabolism genes in children with autism spectrum disorder. *International Journal of Molecular Sciences*, 18(8):1665.
- Chapuy, G. (2007). Random permutations and their discrepancy process. 2007 Conference on Analysis of Algorithms, AofA 07, pages 457–470.
- Chawarska, K., Campbell, D., Chen, L., Shic, F., Klin, A., and Chang, J. (2011). Early generalized overgrowth in boys with autism. *Archives of General Psychiatry*, 68(10):1021–1031.
- Chen, G., Ning, B., and Shi, T. (2019). Single-cell RNA-seq technologies and related computational data analysis. *Frontiers in Genetics*, 10:317.
- Chen, J. (2017). Consistency of the MLE under mixture models. Statistical Science, 32(1):47–63.
- Chung, E. and Romano, J. P. (2013). Exact and asymptotically robust permutation tests. *Annals of Statistics*, 41(2):484–507.
- Cover, T. M. and Thomas, J. A. (2006). Elements of Information Theory. Wiley-Interscience, 2nd edition.
- Dadaneh, S. Z., Qian, X., and Zhou, M. (2018). BNP-seq: Bayesian nonparametric differential expression analysis of sequencing count data. *Journal of the American Statistical Association*, 113(521):81–94.
- Deb, N. and Sen, B. (2021). Multivariate rank-based distribution-free nonparametric testing using measure transportation. *Journal of the American Statistical Association*, (in press).
- Ezegwui, I., Lawrence, L., Aghaji, A., Obiekwe, O., Okoye, O., Onwasigwe, E., and Ebigbo, P. (2014). Refractive errors in children with autism in a developing country. *Nigerian Journal of Clinical Practice*, 17:467–70.
- Fedorov, V. (1972). Theory of Optimal Experiments Designs. Academic Press.
- Fisher, R. A. (1925). Statistical Methods for Research Workers. Oliver and Boyd.
- Fisher, R. A. (1935). Design of Experiments. Oliver and Boyd.
- Fukumoto, A., Hashimoto, T., Mori, K., Tsuda, Y., Arisawa, K., and Kagami, S. (2011). Head circumference and body growth in autism spectrum disorders. *Brain and Development*, 33(7):569–75.

- Han, Y. and Shiragur, K. (2020). The optimality of profile maximum likelihood in estimating sorted discrete distributions. arXiv preprint arXiv:2004.03166.
- Hengartner, N. W. (1997). Adaptive demixing in Poisson mixture models. Annals of Statistics, 25(3):917–928.
- Hoeffding, W. (1952). The large-sample power of tests based on permutations of observations. *Annals of Mathematical Statistics*, pages 169–192.
- Hohn, V. D., de Veld, D., Mataw, K., van Someren, E., and Begeer, S. (2019). Insomnia severity in adults with autism spectrum disorder is associated with sensory hyper-reactivity and social skill impairment. *Journal of Autism and Developmental Disorders*, 49(5):2146–2155.
- Hoirisch-Clapauch, S. and Nardi, A. (2019). Autism spectrum disorders: Let's talk about glucose? *Translational Psychiatry*, 9(1):51.
- Huang, M., Wang, J., Torre, E., Dueck, H., Shaffer, S., Bonasio, R., Murray, J., Raj, A., Li, M., and Zhang, N. R. (2018). SAVER: Gene expression recovery for UMI-based single cell RNA sequencing. *bioRxiv*.
- Jewell, N. P. (1982). Mixtures of exponential distributions. Annals of Statistics, 10(2):479-484.
- Jiang, W. and Zhang, C.-H. (2019). Rate of divergence of the nonparametric likelihood ratio test for gaussian mixtures. *Bernoulli*, 25(4B):3400–3420.
- Jiao, J., Han, Y., and Weissman, T. (2018). Minimax estimation of the L_1 distance. *IEEE Transactions on Information Theory*, 64(10):6672–6706.
- Jiao, J., Venkat, K., Han, Y., and Weissman, T. (2015). Minimax estimation of functionals of discrete distributions. *IEEE Transactions on Information Theory*, 61(5):2835–2885.
- Joshi, G., Biederman, J., Petty, C., Goldin, R. L., Furtak, S. L., and Wozniak, J. (2012). Examining the comorbidity of bipolar disorder and autism spectrum disorders: A large controlled analysis of phenotypic and familial correlates in a referred population of youth with bipolar I disorder with and without autism spectrum disorders. *Journal of Clinical Psychiatry*.
- Kiefer, J. and Wolfowitz, J. (1956). Consistency of the maximum likelihood estimator in the presence of infinitely many incidental parameters. *Annals of Mathematical Statistics*, 27(4):887–906.
- Laird, N. (1978). Nonparametric maximum likelihood estimation of a mixing distribution. *Journal of the American Statistical Association*, 73(364):805–811.
- Lambert, D. and Tierney, L. (1984). Asymptotic properties of maximum likelihood estimates in the mixed Poisson model. *Annals of Statistics*, 12(4):1388–1399.
- Lesperance, M. L. and Kalbfleisch, J. D. (1992). An algorithm for computing the nonparametric mle of a mixing distribution. *Journal of the American Statistical Association*, 87(417):120–126.
- Lindsay, B. G. (1983a). The geometry of mixture likelihoods: A general theory. *Annals of Statistics*, 11(1):86–94.
- Lindsay, B. G. (1983b). The geometry of mixture likelihoods, part II: The exponential family. *Annals of Statistics*, 11(3):783–792.

- Lindsay, B. G. (1995). Mixture models: Theory, geometry and applications. NSF-CBMS Regional Conference Series in Probability and Statistics, 5:I-163.
- Lindsay, B. G. and Roeder, K. (1993). Uniqueness of estimation and identifiability in mixture models. Canadian Journal of Statistics, 21(2):139–147.
- Liu, S., Jiang, Y., and Yu, T. (2019). Modelling RNA-Seq data with a zero-inflated mixture Poisson linear model. *Genetic Epidemiology*, 43(7):786–799.
- Loh, W.-L. and Zhang, C.-H. (1996). Global properties of kernel estimators for mixing densities in discrete exponential family models. *Statistica Sinica*, 6(3):561–578.
- Love, M., Huber, W., and Anders, S. (2014). Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biology*, 15:550.
- Lu, M. (2018). Generalized Adaptive Shrinkage Methods and Applications in Genomics Studies. University of Chicago.
- Marascuilo, L. A. and McSweeney, M. (1977). Nonparametric and Distribution-Free Methods for the Social Sciences. Brooks/Cole Publishing Company.
- Mardia, J., Jiao, J., Tànczos, E., Nowak, R. D., and Weissman, T. (2019). Concentration inequalities for the empirical distribution of discrete distributions: Beyond the method of types. *Information and Inference:* A Journal of the IMA, 9(4):813–850.
- Mielke, P. W. and Berry, K. J. (2007). Permutation Methods: A Distance Function Approach. Springer.
- Mielke Jr, P. (1984). 34 Meteorological applications of permutation techniques based on distance functions. In *Handbook of Statistics*, volume 4, pages 813–830. Elsevier.
- Mielke Jr, P. W., Berry, K. J., and Johnson, E. S. (1976). Multi-response permutation procedures for a priori classifications. *Communications in Statistics-Theory and Methods*, 5(14):1409–1424.
- Nguyen, X. et al. (2013). Convergence of latent mixing measures in finite and infinite mixture models. *Annals of Statistics*, 41(1):370–400.
- Panaretos, V. M. and Zemel, Y. (2019). Statistical aspects of Wasserstein distances. *Annual Review of Statistics and Its Application*, 6(1):405–431.
- Petersen, A. and Müller, H.-G. (2019). Fréchet regression for random objects with Euclidean predictors.

 Annals of Statistics, 47(2):691–719.
- Pfanzagl, J. (1988). Consistency of maximum likelihood estimators for certain nonparametric families, in particular: Mixtures. *Journal of Statistical Planning and Inference*, 19(2):137–158.
- Pitman, E. J. G. (1938). Significance tests which may be applied to samples from any populations III. The analysis of variance test. *Biometrika*, 29(3/4):322–335.
- Polyanskiy, Y. and Wu, Y. (2020). Self-regularizing property of nonparametric maximum likelihood estimator in mixture models. arXiv preprint arXiv:2008.08244.

- Rau, A., Maugis-Rabusseau, C., Martin-Magniette, M.-L., and Celeux, G. (2015). Co-expression analysis of high-throughput transcriptome sequencing data with Poisson mixture models. *Bioinformatics*, 31(9):1420–1427.
- Rebafka, T. and Roueff, F. (2015). Nonparametric estimation of the mixing density using polynomials. Mathematical Methods of Statistics, 24:200–224.
- Robinson, J. (1973). The large-sample power of permutation tests for randomization models. *Annals of Statistics*, 1(2):291–296.
- Robinson, M. D., McCarthy, D. J., and Smyth, G. K. (2010). edgeR: a Bioconductor package for differential expression analysis of digital gene expression data. *Bioinformatics*, 26(1):139–140.
- Roueff, F. and Rydén, T. (2005). Nonparametric estimation of mixing densities for discrete distributions.

 Annals of Statistics, 33(5):2066–2108.
- Sarkar, A. K. and Stephens, M. (2021). Separating measurement and expression models clarifies confusion in single cell RNA-seq analysis. *Nature Genetics*.
- Scheffé, H. (1959). The Analysis of Variance. Wiley.
- Serfling, R. J. (1980). Approximation Theorems of Mathematical Statistics. Wiley.
- Shi, H., Drton, M., and Han, F. (2020). Distribution-free consistent independence tests via center-outward ranks and signs. *Journal of the American Statistical Association*, (in press).
- Silva, A., Rothstein, S. J., McNicholas, P. D., and Subedi, S. (2019). A multivariate Poisson-log normal mixture model for clustering transcriptome sequencing data. *BMC Bioinformatics*, 20:394.
- Simar, L. (1976). Maximum likelihood estimation of a compound Poisson process. *Annals of Statistics*, 4(6):1200–1209.
- Still, A. and White, A. (1981). The approximate randomization test as an alternative to the F test in analysis of variance. *British Journal of Mathematical and Statistical Psychology*, 34(2):243–252.
- Tian, K., Kong, W., and Valiant, G. (2017). Learning populations of parameters. arXiv preprint arXiv:1709.02707.
- Timan, A. F. (2014). Theory of Approximation of Functions of A Real Variable. Elsevier.
- van de Geer, S. (1996). Rates of convergence for the maximum likelihood estimator in mixture models. Journal of Nonparametric Statistics, 6(4):293–310.
- van de Geer, S. (2003). Asymptotic theory for maximum likelihood in nonparametric mixture models. Computational Statistics and Data Analysis, 41(3):453–464.
- Velmeshev, D., Schirmer, L., Jung, D., Haeussler, M., Perez, Y., Mayer, S., Bhaduri, A., Goyal, N., Rowitch, D. H., and Kriegstein, A. R. (2019). Single-cell genomics identifies cell type-specific molecular changes in autism. *Science*, 364(6441):685–689.
- Vinayak, R. K., Kong, W., Valiant, G., and Kakade, S. (2019). Maximum likelihood estimation for learning populations of parameters. In *International Conference on Machine Learning*, volume 97, pages 6448–6457.

- Vu, T. N., Wills, Q. F., Kalari, K. R., Niu, N., Wang, L., Rantalainen, M., and Pawitan, Y. (2016). Beta-Poisson model for single-cell RNA-seq data analyses. *Bioinformatics*, 32(14):2128–2135.
- Wu, C.-F. (1978a). Some algorithmic aspects of the theory of optimal designs. *Annals of Statistics*, 6(6):1286–1301.
- Wu, C.-F. (1978b). Some iterative procedures for generating nonsingular optimal designs. *Communications in Statistics-Theory and Methods*, 7(14):1399–1412.
- Wu, H., Qin, Z., and Zhu, Y. (2013). PM-seq: Using finite Poisson mixture models for RNA-seq data analysis and transcript expression level quantification. *Statistics in Biosciences*, 5:71–87.
- Wu, Y. and Yang, P. (2016). Minimax rates of entropy estimation on large alphabets via best polynomial approximation. *IEEE Transactions on Information Theory*, 62(6):3702–3720.
- Wu, Y. and Yang, P. (2020a). Optimal estimation of gaussian mixtures via denoised method of moments.

 Annals of Statistics, 48(4):1981–2007.
- Wu, Y. and Yang, P. (2020b). Polynomial methods in statistical inference: Theory and practice. Foundations and Trends in Communications and Information Theory, 17(4):402–586.
- Zhang, C.-H. (1995). On estimating mixing densities in discrete exponential family models. *Annals of Statistics*, 23(3):929–945.
- Zhang, M., Liu, S., Miao, Z., Han, F., Gottardo, R., and Sun, W. (2021). Individual level differential expression analysis for single cell RNA-seq data. x(x):1-11.
- Zhang, M. J., Ntranos, V., and Tse, D. (2020). Determining sequencing depth in a single-cell RNA-seq experiment. *Nature Communications*, 11:774.