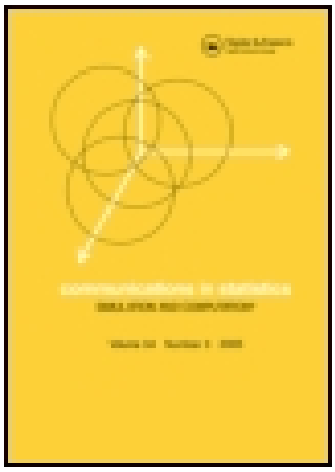

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Sequential Two-stage D-optimality Sensitivity Test for Binary Response Data

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Sequential Two-stage D-optimality Sensitivity Test for Binary Response Data

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Abstract

In order to efficiently extract information about an underlying population based on binary response data (e.g., dead or alive, explode or unexplode), we propose a two-stage D-optimality sensitivity test, which consists of two parts. The first part is a two-stage uniform design used to generate an overlap quickly; the second part conducts the locally D-optimal augmentations to determine optimal follow-up design points. Simulations indicate that the proposed method outperforms the Langlie, Neyer and Dror and Steinberg methods in terms of probability of achieving an overlap and estimation precision. Moreover, the superiority of the proposed method are confirmed by two real applications.

Keywords: Sensitivity; D-optimality; Maximum likelihood estimator; Langlie method; Neyer method; Overlap; Uniform design.

AMS Subject Classification: 62L05; 62K05; 62P10

1 Introduction

Binary response data or dichotomous data are important and commonly used in biology and initiating explosive device study (e.g., dead or alive, exploded or unexploded). Sensitivity refers to the critical value of a latent continuous variable in a binary response data. For example, the critical shock which makes an explosive explode, or the critical dose of a rat poison

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that makes a white rat dead. The problem of interest is to make inferences about the sensitivity distribution. To this end, sensitivity tests are conducted to gather information about the sensitivity.

Sensitivity tests can be applied in various research fields such as biological, pharmaceutical, psychological and engineering research and so on. However, the scarcity of sensitivity information poses a challenge in constructing the efficient sensitivity tests in various settings. The Probit method (Bliss, 1935) and the Bruceton method (Dixon and Mood, 1948) were two primary attempts in this direction, which are simple but inefficient. Robbins and Monro (1951) proposed the Robbins-Monro method to make inferences about sensitivity quantiles, however it can estimate only one quantile at a time. Langlie (1965) proposed a more efficient sensitivity method, i.e., the well-known Langlie method. For recent work about sensitivity tests, we refer the readers to see Einbinder (1974) for the OSTR method, Wu (1985) for the efficient sequential designs with binary data, Neyer (1994) for the D-optimality based sensitivity test (the Neyer method), and Dror and Steinberg (2008) for the generalized linear models (the D-S method). Other discussions can be found in Davis (1971), McLeish and Tosh (1990), Haines *et al.* (2003), Joseph (2004), Karvanen *et al.* (2007), Tian (2009) and Wang *et al.* (2013).

Among others, the Langlie and Neyer methods are the two most widely-used sensitivity tests, and the D-S method is a new general sensitivity test. The Langlie method was developed to find the design points corresponding to 50% responses, so it could provide a good estimation of median but could not provide an ideal estimation of the population variance of a symmetric distribution. Furthermore, it owns blindness in finding the follow-up design points. Unlike the Langlie method, the Neyer method assumes that the sensitivity follows a parametric model and it has a clear goal in finding the follow-up design points. Roughly speaking, it consists of two parts. The first part is designed to make an overlap come up. By the overlap, we mean that there is an overlap between stimuli that produce responses and those that produce non-responses, or more specifically the smallest response is smaller than the largest non-response. The overlap guarantees the existence of a maximum likelihood estimator (MLE) of the unknown parameters

(see Silvapulle, 1981), which will be used in the second part. In the second part, by maximizing the determinant of the Fisher information matrix of the parameters, it renders the resulting MLEs to have approximately the smallest variances (see Abdelbasit and Plackett, 1983) or provides the smallest confidence ellipsoid for the parameters (See Wu, 1985; McLeish and Tosh, 1990).

Intuitively, the Neyer method is more efficient than the Langlie method. The efficiency of the Neyer method is mainly due to the second part, which can extract as much information as possible from a sensitivity population. However, the cost is that the Neyer method needs to specify one more quantity σ_{guess} — a guess value of the standard deviation— at the beginning. It can be expected that the choice of such a guess value may affect the performance of the Neyer method, which will be seen from our simulation results: a bad guess value σ_{guess} often makes an overlap come up late, resulting in a waste of samples. In practice, it is not easy to give an accurate guess value of the standard deviation, which plays down the efficiency of the Neyer method.

In addition, Dror and Steinberg (2008) considered the problem of experimental design when the response is modeled by a generalized linear model, which could also be applied to multifactor experiments. Based on the D-optimality criterion and Bayesian analysis that exploits a discretization of the parameter space to efficiently represent the posterior distribution, the D-S method uses the posterior medians as the estimators and shows some superiorities in efficiency to the Neyer and Bruceton methods. However, this method typically includes more than just two inputs, and the selection of the prior distributions is also need to be discussed. The priors are obviously important and may affect the performance of the D-S method, which will be seen from our simulation results.

As pointed out earlier, an efficient sensitivity test should require less initial knowledge of the parameters and use all the current data information to determine the next design points. According to the above discussion and motivated by the Neyer and D-S methods, we propose a two-stage D-optimality sensitivity test method in this paper, which consists of two parts. The

first part is designed to generate an overlap and preliminarily estimate the parameters. The second part, similar to the most efficient part of the Neyer and D-S methods, determines the optimal follow-up design points by the D-optimality criterion. The proposed test requires only a lower bound x_L and an upper bound x_U of the mean beforehand. Our simulations indicate the proposed method has larger probabilities of obtaining an overlap and gives better parameter estimates compared with the Langlie, Neyer and D-S methods.

The rest of this paper is organized as follows. In Section 2, we introduce the general idea of the proposed method. The first part of the proposed method is determined specifically in Section 3. Simulations are conducted in Section 4 to compare the proposed method and three competing methods, i.e., the Langlie, Neyer and D-S methods. In Section 5, we apply the proposed method to two real sensitivity products and compare it with the Langlie and Neyer methods again. Section 6 contains a discussion about the proposed method.

2 Two-stage D-Optimality Sensitivity Test

We first present some assumptions on the sensitivity data and then introduce the proposed two-stage D-optimality sensitivity test.

2.1 Model assumption

Due to the scarcity of information, making a direct inference about the sensitivity distribution is difficult. In practice, parametric models are usually assumed based on the historical data or experiences of the investigator. In this paper, as in Silvapulle (1981), Neyer (1991, 1994) and Dror and Steinberg (2008), we assume the cumulative distribution function (CDF) of the sensitivity takes the form $F((x-\mu)/\sigma)$, where $F(\cdot)$ is a known function and μ and $\sigma > 0$ are unknown location and scale parameters, respectively. For simplicity, we focus on the case in which the parameters μ and σ respectively denote the population mean and standard deviation, such as normal and log-normal distributions.

Suppose the experiments have been conducted sequentially at stimuli levels $x_1, x_2, \cdots, x_N$. Let δ_i be the experimental result at x_i, where $\delta_i = 1$ denotes a response and $\delta_i = 0$ a non-response. The likelihood function based on x_i and δ_i $(i = 1, \cdots, N)$ is denoted as

$$L(\mu, \sigma) = \prod_{i=1}^{N} F(z_i)^{\delta_i}(1 - F(z_i))^{1-\delta_i}, \quad z_i = (x_i - \mu)/\sigma. \tag{1}$$

The parameters μ and σ are usually estimated by their MLEs $\hat{\mu}$ and $\hat{\sigma}$, respectively (Silvapulle, 1981). Any function of μ and σ, for instance $h(\mu, \sigma)$, can also be estimated by its MLE $h(\hat{\mu}, \hat{\sigma})$. Take a quantile of the sensitivity distribution for example. Let L_q be the qth percentile of the sensitivity distribution and z_q be the solution to $F(z_q) = q$. Then L_q can be estimated by $\hat{L}_q = \hat{\mu} + z_q\hat{\sigma}$.

2.2 The D-Optimality part

The proposed test consists of two parts: an initial part and a D-optimality part. The initial part is designed to find an overlap and preliminary estimate the parameters. The D-optimality part follows the initial part and is designed to determine the optimal follow-up design points. We first introduce the D-optimality part since it is similar to the main part of the Neyer and D-S methods. The initial part will be presented in the next subsection.

The Fisher Information Matrix The Fisher information is a measure of the amount of information that the data carry about an unknown parameter. Let (x_i, δ_i) $(i = 1, 2, \cdots, n)$ be the first n experimental data, then the Fisher information matrix of the parameter $\theta = (\mu, \sigma)$ under the parametric model $F((x - \mu)/\sigma)$ is

$$I_n(\theta) = \begin{pmatrix} I_{11} & I_{12} \\ I_{21} & I_{22} \end{pmatrix} = \sum_{i=1}^{n} \frac{(F'(z_i))^2}{F(z_i)(1 - F(z_i))\sigma^2} \begin{pmatrix} 1 & z_i \\ z_i & z_i^2 \end{pmatrix}, \tag{2}$$

where $F'(\cdot)$ denotes the derivative of $F(\cdot)$, $z_i = (x_i - \mu)/\sigma,\ i = 1, \cdots, n$.

The D-optimality part Suppose an overlap comes up after the first n experiments have been conducted in the initial part. Denote $\hat{\theta}_n$ as the MLE of θ based on the first n observations. It is well-known that $\hat{\theta}_n - \theta$ is approximately distributed as $\mathrm{N}\left(0, I_n^{-1}(\theta)\right)$ as $n \to \infty$, and the determinant $|I_n^{-1}(\theta)|$ measures that dispersion of $\hat{\theta}_n$.

With the purpose of minimizing the dispersion of $\hat{\theta}_{n+1}$, we determines the $(n+1)$th design point in the D-optimality part by

$$x_{n+1} = \arg\max_{x} |I_{n+1}(x; \hat{\theta}_n)|, \tag{3}$$

where

$$I_{n+1}(x; \hat{\theta}_n) = I_n(\hat{\theta}_n) + \frac{(F(z)')^2}{F(z)(1-F(z))\hat{\sigma}_n^2} \begin{pmatrix} 1 & z \\ z & z^2 \end{pmatrix}, \ z = (x - \hat{\mu}_n)/\hat{\sigma}_n.$$

The above determination of x_{n+1} is based on the assumption that there is an overlap after the first n experiments in the initial part. If no overlap comes up, then the MLE does not exist. In this situation, motivated by Neyer (1994), we define $\hat{\theta}_n = (\hat{\mu}_n, \hat{\sigma}_n)$ in (2) as follows,

$$\begin{cases} \hat{\mu}_n = \dfrac{x_{1L}^{(n)} + x_{0U}^{(n)}}{2}, \\ \hat{\sigma}_n = x_{1L}^{(n)} - x_{0U}^{(n)}, \end{cases} \tag{4}$$

where $x_{0U}^{(n)}$ and $x_{1L}^{(n)}$ are the largest non-response and the smallest response of the first n data. If $x_{0U}^{(n)}$ or $x_{1L}^{(n)}$ has no definition, i.e., all experiments respond or none respond, we set $x_{0U}^{(n)} = x_L$ or $x_{1L}^{(n)} = x_U$.

If the parameter of interest is only $\theta = \mu$ or $\theta = \sigma$, we need to modify the above procedure by replacing $I_n(\theta)$ with $(I_{11}I_{22} - I_{12}^2)/I_{22}$ or $(I_{11}I_{22} - I_{12}^2)/I_{11}$, respectively.

2.3 The initial part

We design the initial part by combining the following three considerations. First, it should obtain an overlap quickly, since the existence of the MLE is based on the existence of the overlap. Second, as the D-optimality part is efficient for the moderate and large sample size, the number of design points in the initial part should not be too small (preferably larger than 5). At last, considering the cost of the experiments, the number of design points in the initial part should not be too large (preferably less than 10).

The premise of conducting the initial part is to specify the lower and upper bounds of the mean, x_L and x_U, which gives a non-response and a response respectively. In practice, x_L

and x_U are often conservatively determined according to the practitioner's experience such that almost surely the stimulus level x_L produces a non-response, and x_U produces a response. Here, we provide a possible way to specify the lower and upper bounds. Suppose the sensitivity has a natural lower bound $x_{\min} > -\infty$ and a natural upper bound $x_{\max} < \infty$. We select two stimuli levels x_L and x_U ($x_{min} \le x_L < x_U \le x_{max}$) and conduct experiments at them. The lower and upper bounds x_L and x_U are determined if we observe one non-response and one response. Otherwise, if the experiments all give responses, we replace x_L with $\max\{2x_L - x_U, x_{\min}\}$ and conduct experiment at the new x_L. This procedure may be iterated many times until a non-response is observed at the resulting x_L. The case that all experiment produces non-responses can be treated in the same way. According to our simulation experiences, if a probit model is appropriate for the underlying sensitivity, we recommend choosing $x_L = \tilde{\mu} - k\tilde{\sigma}$ and $x_U = \tilde{\mu} + k\tilde{\sigma}$ for some $k > 0$. Here $\tilde{\mu}$ and $\tilde{\sigma}$ are respectively the best current estimates of the mean μ and the standard deviation σ that the experimenters obtain. We recommend $k = 3$ if only μ is of interest, and $k = 5$ when the parameter of interest is σ or both μ and σ. Under a probit sensitivity model, any parameter of the sensitivity is a smooth function of μ and σ, and therefore can be estimated through the estimates of μ and σ. Conservatively, we also recommend the choice $k = 5$ for other parameters such as quantiles.

For convenience, we proceed with the premise that the lower and upper bounds x_L and x_U are determined. We first conduct n_1 experiments equally spreading in the interval (x_L, x_U) and check whether an overlap comes up. If the overlap appears, turn to the D-optimality part; otherwise, conduct n_2 experiments equally spreading in the interval $(x_{0U}^{(n_1)}, x_{1L}^{(n_1)})$, where $x_{0U}^{(n_1)}$ and $x_{1L}^{(n_1)}$ denote the largest non-response and the smallest response of the first n_1 data. This process may be iterated several times. We call the experiments before the D-optimality part an initial test; The number of iterations in the initial test and the number of runs needed in each iteration will be determined in the next section. In general, if no overlap comes up in the initial test, then the proposed guess value $\hat{\sigma}_n$ in (3) is most likely smaller than σ. Having approximately equal numbers of runs in each stage of the initial design is the most efficient

way to decrease the guessed value in this situation. A note to the practitioners is that if they really are unsure about σ, they should run a larger initial experiment until they are certain that the guessed value in (3), despite no overlap, is not larger than σ.

Specifically, we consider the following choices for the initial part.

1) **One-stage uniform design.** Let n_1 be a pre-specified integer. We first conduct n_1 experiments at design points

$$x_j = x_L + j \cdot \frac{x_U - x_L}{n_1 + 1}, \qquad j = 1, 2, \cdots, n_1,$$

and then turn to the D-optimality part. These design points are called a one-stage uniform design as they are uniformly spaced.

2) **Two-stage uniform design.** We first conduct a one-stage uniform design with n_1 experiments in the interval (x_L, x_U) and check whether an overlap comes up. If the overlap comes up, turn to the D-optimality part. Otherwise, we conduct another one-stage uniform design with n_2 experiments in the interval $(x_{0U}^{(n_1)}, x_{1L}^{(n_1)})$, and then turn to the D-optimality part.

3) **Multiple-stage uniform design.** Similar to a two-stage uniform design, we can get a multiple-stage uniform design by iterating the one-stage uniform design several times.

We may adopt a multiple-stage uniform design in the initial part. However, considering the experimental cost and complexity, we do not recommend more-than-three-stages uniform designs in practice.

3 Choice for the initial part

We have presented several choices for the initial part. In this section, through simulations we determine: 1) the number of stages and 2) the sample sizes in each stage. To illustrate the main idea of the proposed method, we assume the sensitivity follows a normal distribution which

is the most important. Without loss of generality, in what follows we assume that the true sensitivity model is N(0, 1).

3.1 Choice for the number of stage

The main purpose of the initial part is to find an overlap quickly. We now compare the one-stage, two-stage and three-stage uniform designs from the viewpoint of achieving an overlap.

To proceed, we present a definition of the term "overlap". Given a series of sensitivity data (X_i, δ_i) $(i = 1, 2, \cdots, n)$, let $X_{0U}^{(n)}$ and $X_{1L}^{(n)}$ denote the largest stimulus that produces a non-response and the smallest stimulus that produces a response, respectively. We say that an overlap comes up, if and only if $X_{0U}^{(n)} > X_{1L}^{(n)}$. Thus the probability of achieving an overlap after n experiments is defined as $P(X_{0U}^{(n)} > X_{1L}^{(n)})$. If $X_{0U}^{(n)}$ or $X_{1L}^{(n)}$ has no definition, i.e., all experiments respond or none respond, then no overlap comes up.

We considered 64 pairs of x_L and x_U in our simulations with x_L being integers between -10 and -3, and x_U being integers between 3 and 10. Let n_1, n_2 and n_3 denote the number of experiments in the first, second and third stages, respectively. The total sample size of the initial part, $n_1 + n_2 + n_3$, is chosen to be between 6 and 9. For a fixed total sample size such as 9, if a two-stage uniform design is considered, we take the largest probability of achieving an overlap among all combinations $\{(n_1, n_2) : n_1 + n_2 = 9\}$ as the probability of this design at the sample size 9. Three-stage uniform designs are treated similarly. All such probabilities are shown in Figure 1 based on 10,000 replications.

After carefully studying Figure 1, we have the following findings. Firstly, for all the combinations of $[x_L, x_U]$, the two-stage uniform designs have a significant increase in the probability of achieving an overlap compared with the one-stage uniform designs. The increase is about 10% when the total sample size is 6 or 7, and is more than 20% when the total sample size is 8 or 9. Secondly, the three-stage uniform designs have the larger probabilities of achieving an overlap than the two-stage uniform designs. However, this increase is very limited, mostly less than 5%. Thirdly, the probabilities of the three designs get larger as the total sample size

increases.

According to the above discussion, we exclude the one-stage uniform design because its probability of achieving an overlap is significantly less than the two-stage uniform design. The three-stage uniform design is also not acceptable, since its probability of achieving an overlap is slight larger than the two-stage uniform design at the cost of much complication. Thus, we choose the two-stage uniform design for the initial part since it is simple and effective.

3.2 Choice for sample size combination

In this subsection, we determine the sample size pair (n_1, n_2) of the two-stage uniform design from the viewpoint of the estimation precision by simulations. Let $\hat{\theta}$ be the MLE of the parameter θ, which may be $\theta = (\mu, \sigma)$, $\theta = \mu$ or $\theta = \sigma$. Define the sum of squared bias (SSB) as

$$\text{SSB}_\theta \equiv \frac{\|\theta - \hat{\theta}\|^2}{\sigma^2},$$

where σ is the standard deviation. We take the average of SSB_θ, denoted MSE_θ (mean squared error), as the criteria of evaluating estimation precision.

In the simulations, we consider four typical choices of $[x_L, x_U]$, i.e., $[-3, 3]$, $[-3, 5]$, $[-5, 10]$ and $[-8, 10]$. Ten reasonable sample size pairs (n_1, n_2) are chosen, and N is 25 and 30. We generate 2,000 data-sets and estimate $\theta = (\mu, \sigma)$ by the strategy used in the D-optimality part of the proposed method.

The simulation results are presented in Tables 1 and 2. In general, the combinations $(3, 4)$ and $(3, 3)$ of (n_1, n_2) give the smallest values of $\text{MSE}_{(\mu,\sigma)}$. Furthermore, the results in subsection 3.1 indicate that the probability of achieving an overlap gets larger as the total sample size increases. Thus, we finally choose $(n_1, n_2) = (3, 4)$ as the sample size pair in the two-stage uniform design.

Thereafter, we have completely determined the proposed sensitivity test, which implements the two-stage uniform design with the sample size pair $(3, 4)$ in the initial part and then follows by the D-optimality part until the number of experiments n is equal to the sample size N.

4 Simulation study

In this section, performances of the proposed method are evaluated through Monte Carlo simulations compared with the Langlie, Neyer and D-S methods. The principal criterions are the probability of achieving an overlap and estimation precision.

4.1 Probability of obtaining an overlap

According to Silvapulle (1981), unique MLEs exist if and only if the sensitivity data produce an overlap. Thus, the probability of obtaining an overlap is regarded as a general criteria of evaluating different test methods.

Since all the methods need a lower bound x_L and an upper bound x_U of the mean, four arbitrary choices of $[x_L, x_U]$ are considered in our simulations, i.e., $[-3, 3]$, $[-3, 4]$, $[-4, 4]$ and $[-4, 7]$. Besides, noting that the Neyer test depends on σ_{guess}, we consider two choices of σ_{guess}, i.e., 1 and 3 (ND1, ND3 for short). For the D-S method, we need to determine the prior distributions for μ and σ. As Dror and Steinberg (2008) advised making the spread of the prior large for the D-S method, a natural choice of the prior distributions are

$$\mu \sim \mathrm{N}(\mu_1, \sigma_1^2), \quad \sigma \sim \mathrm{lognormal}(\log(\mu_2), \sigma_2^2),$$

where $\mu_1 = 0.5(x_L + x_U)$ and $\mu_2 = 0.1(x_U - x_L)$. In order to guarantee almost surely that the stimulus x_U will produce a response and the stimulus x_L won't produce a response, we choose the prior variances σ_1^2 and σ_2^2 such that $F(x_L)$ is very close to 0 and $F(x_U)$ is very close to 1 (e.g., 95%). We consider four choices of (σ_1, σ_2): (I) $((x_U - x_L)/3,\ \mu_2/3)$; (II) $((x_U - x_L)/4,\ \mu_2/4)$; (III) $((x_U - x_L)/6,\ \mu_2/2)$ and (IV) $((x_U - x_L)/10,\ \mu_2/2)$, and calculate the probabilities of achieving an overlap based on 10,000 replications. The simulation results are shown in Figure 2, where the probabilities of the D-S method are based on the priors (IV) (Source code can be found *http://www.math.tau.ac.il/~dms/GLM_Design*).

When the sample size is less than 10, the ND1 and D-S methods have the largest proba-

bilities of all; the proposed method is slightly less than the Langlie method, but larger than the ND3 method. When the sample size is larger than 10, the proposed method has the largest probabilities; the ND1 and D-S follow; the Langlie and ND3 methods have the least probabilities. Since the sample size is usually more than 10 in practice, the proposed method is promising and the best from the viewpoint of probability of achieving an overlap, compared with the Langlie, Neyer and D-S methods. Meanwhile, it is also seen that the performance of the Neyer method is affected by σ_{guess}.

4.2 Estimation precision

As shown above, the ND3 method is inferior to the ND1 method. In this subsection, we compare the proposed method only with the Langlie, ND1 and D-S methods according to the MSE_θ.

Besides the MSE_θ, in order to assess the overall performance between different settings, we can apply the relative mean index (RMI) which was used by Han and Tsung (2006), Zou and Qiu (2009). We define

$$\mathrm{RMI}_\theta = \frac{1}{K}\sum_{i=1}^{K}\frac{\mathrm{MSE}_\theta^{(i)} - \mathrm{SMSE}_\theta^{(i)}}{\mathrm{SMSE}_\theta^{(i)}},$$

where $\mathrm{SMSE}_\theta^{(i)}$ is the smallest $\mathrm{MSE}_\theta^{(i)}$ of the i-th setting ($i = 1, \cdots, K$) among all the test methods (i.e., the Langlie, the Neyer, the D-S and the proposed methods). Then, $(\mathrm{MSE}_\theta^{(i)} - \mathrm{SMSE}_\theta^{(i)})/\ \mathrm{SMSE}_\theta^{(i)}$ can be considered as a relative efficiency measure of the $\mathrm{MSE}_\theta^{(i)}$, compared to the best one, and RMI_θ is the average of all the relative efficiency values. A test plan with a smaller RMI_θ value is considered better in its overall performance.

In this simulation, we choose ten pairs of $[x_L, x_U]$, i.e., $[-3, 3]$, $[-3, 5]$, $[-4, 4]$, $[-4, 6]$, $[-4, 8]$, $[-5, 5]$, $[-5, 7]$, $[-5, 10]$, $[-6, 6]$, $[-8, 10]$ and $N = 20$, 25, 30 and 40. We compare three types of parameters, i.e., $\theta = (\mu, \sigma)$, $\theta = \mu$ and $\theta = \sigma$. The corresponding simulation results based on 2,000 replications are presented in Tables 3-6, respectively.

In the case of $\theta = (\mu, \sigma)$, the MSE_μ and MSE_σ are listed separately in Tables 3-4. The

results of the D-S method based on the four priors are shown in Appendix A, where we can see that the D-S method is affected by the priors. The results of the D-S method in Tables 3-4 are all from the priors (IV).

On the one hand, if we compare the four methods in estimating μ and σ together, by using $\text{MSE}_{(\mu,\sigma)}= \text{MSE}_{\mu}+\text{MSE}_{\sigma}$, it is easy to see the proposed method always has the least $\text{RMI}_{(\mu,\sigma)}$, and the D-S method performs better than the ND1 when the sample size is small. On the other hand, if we compare these methods in estimating μ and σ, respectively, we find the langlie method and the D-S method perform better than others from Tables 3-4.

Since the D-S method relies on the priors and the computations are complicated, in the case of $\theta = \mu$ and $\theta = \sigma$, we only compare the ND1 and our methods based on 2,000 replications, where the $I_n(\theta; x)$ should be replaced with $(I_{11}I_{22} - I_{12}^2)/I_{22}$ and $(I_{11}I_{22} - I_{12}^2)/I_{11}$, respectively.

In the case of $\theta = \mu$, the two methods have similar and nice performances according to the MSE_{μ}, which are shown in Table 5. Note that when we focus on $\theta = \mu$, the MSE_{μ}s of the ND1 and our method are all smaller than those in Table 3, where we focus on $\theta = (\mu, \sigma)$. Moreover, these two methods perform better than the Langlie method according to the RMI_{μ}.

In the case of $\theta = \sigma$, according to the RMI_{σ}, the proposed method has uniformly better estimation precision than the Langlie method and has comparable results with the ideal ND1 method. For reasonable comparison, we add the simulation results of the Neyer method with $\sigma_{guess} = 1.5$ (ND1.5 for short) in Table 6. It can be seen that the proposed method has better estimation precision than the ND1.5. And the ND1.5 is severely inferior to the ND1 although $\sigma_{guess} = 1.5$ is very close to the true value. In addition, when we focus on $\theta = \sigma$, the MSE_{σ}s of ND1 and our method are all smaller than those in Table 4, where we focus on μ and σ together.

5 Two real applications

Cooperating with a sensitivity experimental laboratory, we depict two applications of our proposed method to sensitivity experiment in this section. The experiment's objectives are to estimate the sensitivity parameters of two types of sensitivity products, denoted as type I and

type II.

According to experience, it is sensible to assume that the sensitivities of the two types of products follow the normal distributions. Moreover, the type I product has been studied before and the laboratory has historical information about its sensitivity (the true values of μ and σ are about 9.3 and 0.3, respectively). While, the type II product is new. We apply the Langlie, Neyer methods and our proposed method to the type I and type II products.

For the type I product, the lower and the upper bounds are set to be 7.5 and 11.3, and $\sigma_{guess} = 0.3$ in the Neyer method. We conduct one experiment at sample size $N = 15$ and two experiments at $N = 25$. The two larger data sets at sample size $N = 25$ are not augmented from the earlier small ones at sample size $N = 15$. These data sets are produced in a completely independent manner. The estimates of the three methods are presented in Table 7.

It can be seen that all the three methods give very accurate estimates of the location parameter μ. However, the estimates of the parameter σ based on the Langlie or the Neyer methods may deviate severely from the approximate true value 0.3. For example, when $N = 15$ the Neyer method estimates σ by 0.0306; when $N = 25$ the estimate based on the Langlie method is 0.0283. These two poor estimates must correspond to the data set with almost no overlap. As an advantage over the rest two methods, it is easy to see that the proposed method always gives very close estimates to 0.3. Thus we conclude that the new method is more efficient and stable than the Langlie and Neyer methods in practice.

For the type II product, the only information we know is that the estimate of σ is greater than 5. In this case, the Neyer and the proposed methods are our best choices. We conduct one experiment with $N = 20$ for the two methods. The lower and upper bounds are set as 50 and 100, and $\sigma_{guess} = 5$.

The estimates of the Neyer and the proposed methods are $\hat{\mu} = 75.08$, $\hat{\sigma} = 0.39$ and $\hat{\mu} = 68.75$, $\hat{\sigma} = 7.50$, respectively. The estimates of μ are close to each other. However, the Neyer method significantly underestimates σ. While the estimate $\hat{\sigma}_2 = 7.50$ based on the proposed method is more sensible. These results again provide evidence that the proposed method is

very efficient and robust.

6 Discussion

In this paper, under a location-scale distributional assumption on the sensitivity of interest, we propose a two-stage D-optimality sensitivity test method to efficiently extract information from the underlying population; the maximum likelihood method is then employed to estimate the parameters. It is worthwhile to point out that the proposed test has larger probabilities of achieving an overlap and requires less initial parameters than the Neyer and D-S methods. Intuitively it can be expected that people can make more accurate inferences about the sensitivity of interest at the same sample size using the proposed test than using traditional tests. We provided simulation results and two real applications to investigate the efficiency of the proposed test and the resulting location and scale estimators.

It should be noted that when we determine the initial part of the proposed method, the sensitivity distribution is chosen to be $N(0, 1)$. This implies that the choices of two-stage uniform design and sample size pair $(3, 4)$ for the two-stages depends on $N(0, 1)$. When the sensitivity follows a normal or lognormal distribution with arbitrary parameters, we can transform the sensitivity distribution to be $N(0, 1)$. Then the two-stage uniform design and sample size pair $(3, 4)$ are still the best choices. When the sensitivity distribution is not normal or transformed normal distribution, the choices of two-stage uniform design and sample size pair $(3, 4)$ may not be the best. In this situation, we can choose by simulations the number of stages and the sample sizes in the initial test.

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Appendix A. MSE_μ and MSE_σ of the four priors when the parameter of interest is $\theta = (\mu, \sigma)$

For the four priors of the D-S methods in Section 4, the corresponding simulation results on estimation precision based on 2,000 replications are presented in Tables 8-9.

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Table 1: $MSE_{(\mu,\sigma)}$ of sample size combination, $N = 25$.

(n_1, n_2)	$[x_L, x_U]$=			
	[–3, 3]	[–3, 5]	[–5, 10]	[–8, 10]
(3, 3)	0.2305	0.2152	0.2233	0.2023
(3, 4)	0.2269	0.2188	0.2163	0.2138
(4, 3)	0.2503	0.2373	0.2308	0.2128
(4, 4)	0.2445	0.2313	0.2302	0.2309
(4, 5)	0.2533	0.2399	0.2463	0.2290
(5, 3)	0.2517	0.2783	0.2358	0.2388
(5, 4)	0.2531	0.2431	0.2505	0.2668
(5, 5)	0.2484	0.2570	0.2743	0.2575
(6, 3)	0.2456	0.2630	0.2586	0.2433
(6, 4)	0.2536	0.2535	0.2623	0.2725

Table 2: $MSE_{(\mu,\sigma)}$ of sample size combination, $N = 30$.

(n_1, n_2)	$[x_L, x_U]$=			
	[–3, 3]	[–3, 5]	[–5, 10]	[–8, 10]
(3, 3)	0.2063	0.1914	0.1609	0.1713
(3, 4)	0.1801	0.1808	0.1779	0.1794
(4, 3)	0.2132	0.1797	0.1891	0.1933
(4, 4)	0.2124	0.2063	0.2013	0.1773
(4, 5)	0.1957	0.1973	0.1929	0.2000
(5, 3)	0.2008	0.2082	0.2041	0.1925
(5, 4)	0.2169	0.1980	0.2130	0.2045
(5, 5)	0.1873	0.2095	0.2173	0.1992
(6, 3)	0.1983	0.2006	0.2047	0.2092
(6, 4)	0.2095	0.2233	0.2120	0.2149

Table 3: MSE_μ ($\times 10^{-2}$) and RMI_μ when the parameter of interest is $\theta = (\mu, \sigma)$

Methods	Langlie	ND1	D-S	Two-stage	Langlie	ND1	D-S	Two-stage
Bounds	N=20				N=25			
[−3, 3]	9.56	12.77	10.58	11.45	7.73	9.39	9.46	9.12
[−3, 5]	11.79	13.58	22.73	12.56	8.88	11.00	18.34	9.94
[−4, 4]	11.43	12.84	14.92	12.50	8.60	10.20	13.30	9.96
[−4, 6]	12.14	12.20	24.38	12.66	8.84	9.76	19.86	10.25
[−4, 8]	11.53	14.05	43.17	13.28	8.69	9.77	34.36	10.23
[−5, 5]	11.47	12.92	17.75	13.38	9.08	9.40	16.53	10.69
[−5, 7]	13.35	13.50	28.10	13.24	10.12	10.90	23.22	10.40
[−5, 10]	12.08	14.28	48.45	14.36	9.49	10.80	36.07	10.96
[−6, 6]	10.82	12.12	20.16	13.90	8.53	9.49	17.40	11.08
[−8, 10]	15.95	14.77	30.95	16.65	11.23	11.10	25.18	12.37
RMI	0.009	0.128	1.173	0.132	0.001	0.123	1.326	0.157
Bounds	N=30				N=40			
[−3, 3]	6.62	7.68	9.15	7.48	4.73	5.45	7.55	5.73
[−3, 5]	7.32	9.64	16.58	8.36	5.31	6.81	13.17	6.44
[−4, 4]	7.19	8.81	11.61	8.34	5.25	6.43	10.16	6.24
[−4, 6]	6.85	8.57	16.34	8.69	5.00	6.37	13.30	6.61
[−4, 8]	7.16	7.88	28.85	8.53	5.15	5.68	19.70	6.41
[−5, 5]	7.44	7.29	14.29	8.95	5.43	5.63	11.33	6.41
[−5, 7]	7.90	9.21	19.07	8.79	5.78	7.09	14.30	6.67
[−5, 10]	7.71	8.99	28.25	9.00	5.55	7.03	20.71	6.34
[−6, 6]	7.32	7.53	14.78	9.19	5.04	5.41	12.43	6.85
[−8, 10]	8.72	9.49	21.76	10.03	6.02	6.61	17.06	7.05
RMI	0.002	0.150	1.423	0.181	0	0.174	1.702	0.219

Table 4: MSE_σ ($\times 10^{-2}$) and RMI_σ when the parameter of interest is $\theta = (\mu,\ \sigma)$

Methods	Langlie	ND1	D-S	Two-stage	Langlie	ND1	D-S	Two-stage
Bounds	N=20				N=25			
[−3, 3]	23.26	19.25	11.14	18.19	18.81	14.69	10.04	13.57
[−3, 5]	22.21	20.35	4.46	15.27	17.46	14.93	4.43	11.94
[−4, 4]	23.17	19.93	4.82	17.06	18.99	15.54	4.54	13.41
[−4, 6]	22.06	18.18	5.93	15.06	16.97	13.59	5.99	12.08
[−4, 8]	23.37	19.66	11.30	14.51	18.49	14.82	10.47	12.13
[−5, 5]	22.95	20.34	6.94	15.98	18.97	16.03	6.90	12.57
[−5, 7]	22.27	19.65	10.26	14.15	16.88	14.47	9.59	11.71
[−5, 10]	23.13	21.07	22.54	12.92	19.24	16.10	17.08	10.66
[−6, 6]	22.76	19.43	10.65	14.68	18.14	15.09	9.38	12.23
[−8, 10]	24.12	20.95	24.79	10.44	18.22	16.10	21.13	9.79
RMI	1.938	1.554	0.212	0.948	1.471	1.054	0.176	0.653
Bounds	N=30				N=40			
[−3, 3]	15.73	11.90	8.91	10.53	13.07	8.22	7.44	7.22
[−3, 5]	14.98	12.05	4.32	9.72	11.97	8.12	4.12	6.83
[−4, 4]	15.53	11.95	4.31	10.40	11.61	7.89	3.73	7.27
[−4, 6]	14.27	10.39	5.74	9.74	11.31	7.38	5.29	7.08
[−4, 8]	16.62	12.12	10.17	9.66	12.93	8.53	8.31	6.76
[−5, 5]	15.82	12.21	6.20	10.41	11.82	8.50	5.84	7.42
[−5, 7]	14.18	11.95	9.65	9.70	11.25	7.83	8.15	7.01
[−5, 10]	16.19	12.65	14.04	8.79	12.00	8.22	9.98	6.78
[−6, 6]	14.36	11.71	8.97	10.34	11.12	7.96	7.67	7.39
[−8, 10]	14.96	13.01	15.67	8.69	11.31	8.95	11.14	6.72
RMI	1.223	0.741	0.145	0.438	1.047	0.408	0.159	0.222

Table 5: MSE_μ ($\times 10^{-2}$) and RMI_μ when the parameter of interest is $\theta = \mu$

Methods	ND1	Two-stage	ND1	Two-stage
Bounds	N=20		N=25	
[−3, 3]	10.69	10.64	8.62	8.58
[−3, 5]	9.75	11.37	7.85	8.68
[−4, 4]	10.69	11.60	8.41	8.86
[−4, 6]	9.74	12.02	7.21	8.80
[−4, 8]	10.57	12.91	7.85	9.30
[−5, 5]	11.11	11.95	8.74	8.75
[−5, 7]	12.51	13.08	9.10	9.74
[−5, 10]	13.72	13.64	9.69	9.14
[−6, 6]	11.19	11.07	8.36	8.52
[−8, 10]	14.08	14.60	9.87	10.50
RMI	0.002	0.086	0.007	0.072
Bounds	N=30		N=40	
[−3, 3]	6.82	7.12	4.77	5.03
[−3, 5]	6.03	6.82	4.24	4.99
[−4, 4]	6.52	7.02	4.38	4.96
[−4, 6]	5.68	6.74	4.22	4.82
[−4, 8]	6.43	7.13	4.96	4.79
[−5, 5]	7.36	6.81	5.06	4.76
[−5, 7]	7.17	7.37	4.65	4.98
[−5, 10]	7.08	7.11	4.62	4.86
[−6, 6]	6.95	6.58	4.69	4.78
[−8, 10]	7.23	7.62	4.98	5.11
RMI	0.014	0.063	0.010	0.067

Table 6: MSE_σ ($\times 10^{-2}$) and RMI_σ when the parameter of interest is $\theta = \sigma$

Methods	ND1	ND1.5	Two-stage	ND1	ND1.5	2-stage
Bounds	N=20			N=25		
[−3, 3]	14.40	22.19	13.87	11.07	17.34	10.61
[−3, 5]	13.34	19.33	13.44	10.01	14.57	10.59
[−4, 4]	13.59	21.61	14.19	10.97	16.37	10.82
[−4, 6]	12.25	19.34	12.23	10.11	14.81	9.76
[−4, 8]	12.26	22.66	11.39	9.85	16.75	9.38
[−5, 5]	13.95	21.30	13.74	10.43	16.30	10.79
[−5, 7]	10.96	21.37	11.80	9.41	15.82	9.58
[−5, 10]	8.54	19.03	10.92	7.77	14.36	9.11
[−6, 6]	11.31	21.63	11.68	9.18	16.53	9.59
[−8, 10]	7.28	19.75	6.82	7.13	14.60	6.91
RMI	0.020	0.875	0.044	0.018	0.691	0.033
Bounds	N=30			N=40		
[−3, 3]	8.88	13.37	8.32	5.96	7.99	5.89
[−3, 5]	7.86	11.11	8.56	6.18	7.19	6.00
[−4, 4]	8.71	12.47	8.66	6.36	7.94	6.13
[−4, 6]	8.46	11.28	7.94	5.62	7.21	5.71
[−4, 8]	8.31	12.91	7.69	5.93	8.00	5.77
[−5, 5]	8.55	12.59	8.63	6.32	7.82	6.23
[−5, 7]	7.87	12.32	7.87	5.43	7.72	5.67
[−5, 10]	6.78	11.29	7.86	5.53	7.34	6.34
[−6, 6]	7.31	12.60	8.23	5.29	7.84	6.03
[−8, 10]	6.64	11.41	6.36	5.70	7.53	5.43
RMI	0.026	0.578	0.038	0.017	0.339	0.035

Table 7: Parameter estimates of type I product

Methods	No.1: N=15		No.2: N=25		No.3: N=25	
	$\hat{\mu}$	$\hat{\sigma}$	$\hat{\mu}$	$\hat{\sigma}$	$\hat{\mu}$	$\hat{\sigma}$
Langlie	9.1673	0.2513	9.2283	0.0283	9.2118	0.3839
Neyer	9.3915	0.0306	9.3041	0.1823	9.3234	0.2946
Two-stage	9.5755	0.3567	9.2653	0.3438	9.3428	0.3003

Table 8: MSE_{μ} ($\times 10^{-2}$) when the concern parameter $\theta = (\mu, \sigma)$

Priors	I	II	III	IIIV	I	II	III	IIIV
Bounds	N=20				N=25			
$[-3, 3]$	24.52	23.38	19.89	10.58	19.72	19.27	16.35	9.46
$[-3, 5]$	27.69	26.27	24.20	22.73	21.97	20.89	20.56	18.34
$[-4, 4]$	27.83	26.95	22.34	14.92	22.60	22.23	19.17	13.30
$[-4, 6]$	30.89	30.09	27.76	24.38	25.04	25.14	23.30	19.86
$[-4, 8]$	33.69	35.51	32.45	43.17	27.51	28.49	27.02	34.36
$[-5, 5]$	31.18	28.25	27.20	17.75	24.81	23.01	22.54	16.53
$[-5, 7]$	34.86	33.07	29.91	28.10	27.19	26.83	24.73	23.22
$[-5, 10]$	38.54	41.25	35.22	48.45	31.20	31.55	26.66	36.07
$[-6, 6]$	34.57	30.95	30.00	20.16	27.57	25.62	23.79	17.40
$[-8, 10]$	43.23	40.86	39.44	30.95	34.08	32.99	31.08	25.18
Bounds	N=30				N=40			
$[-3, 3]$	16.76	16.47	13.84	9.15	13.01	12.54	10.88	7.55
$[-3, 5]$	18.33	17.05	17.95	16.58	13.65	13.61	13.68	13.17
$[-4, 4]$	19.01	18.77	17.28	11.61	14.53	13.95	13.52	10.16
$[-4, 6]$	21.20	21.36	18.96	16.34	16.09	16.52	15.18	13.30
$[-4, 8]$	22.35	22.79	23.17	28.85	16.31	17.23	17.25	19.70
$[-5, 5]$	20.50	19.01	20.11	14.29	14.94	14.41	14.59	11.33
$[-5, 7]$	22.52	22.57	20.85	19.07	16.62	17.12	15.94	14.30
$[-5, 10]$	24.99	26.43	21.96	28.25	18.58	19.87	16.44	20.71
$[-6, 6]$	23.01	22.09	20.14	14.78	17.32	17.03	16.65	12.43
$[-8, 10]$	27.32	27.12	25.74	21.76	20.13	19.39	19.14	17.06

Table 9: MSE_σ ($\times 10^{-2}$) when the concern parameter $\theta = (\mu, \sigma)$

Priors	I	II	III	IIIV	I	II	III	IIIV
Bounds	N=20				N=25			
$[-3,\ 3]$	13.22	14.20	10.85	11.14	12.36	13.64	9.89	10.04
$[-3,\ 5]$	3.45	3.54	4.89	4.46	3.29	3.34	4.76	4.43
$[-4,\ 4]$	3.46	3.44	4.86	4.82	3.32	3.28	4.47	4.54
$[-4,\ 6]$	2.21	1.02	5.85	5.93	2.43	1.18	6.01	5.99
$[-4,\ 8]$	5.97	4.17	10.26	11.30	5.91	3.98	9.48	10.47
$[-5,\ 5]$	2.26	0.98	6.38	6.94	2.57	1.20	6.20	6.90
$[-5,\ 7]$	5.52	4.17	10.25	10.26	5.36	4.05	9.06	9.59
$[-5, 10]$	14.93	14.86	18.73	22.54	12.77	13.08	16.67	17.08
$[-6,\ 6]$	6.14	3.97	10.08	10.65	5.80	3.92	10.00	9.38
$[-8, 10]$	24.55	25.61	26.26	24.79	20.02	20.80	19.82	21.13
Bounds	N=30				N=40			
$[-3,\ 3]$	11.62	13.12	8.94	8.91	10.31	12.18	7.36	7.44
$[-3,\ 5]$	3.20	3.20	4.62	4.32	2.94	2.94	4.36	4.12
$[-4,\ 4]$	3.18	3.08	4.29	4.31	2.95	2.85	4.14	3.73
$[-4,\ 6]$	2.63	1.33	5.95	5.74	2.81	1.51	5.24	5.29
$[-4,\ 8]$	5.95	3.97	9.04	10.17	5.23	3.91	7.38	8.31
$[-5,\ 5]$	2.76	1.37	6.10	6.20	2.83	1.52	5.81	5.84
$[-5,\ 7]$	5.27	3.96	8.61	9.65	4.79	3.77	7.14	8.15
$[-5, 10]$	11.25	11.75	13.10	14.04	8.85	9.44	10.07	9.98
$[-6,\ 6]$	5.71	3.85	8.99	8.97	5.04	3.58	7.23	7.67
$[-8, 10]$	16.36	17.63	15.88	15.67	11.63	13.06	11.83	11.14

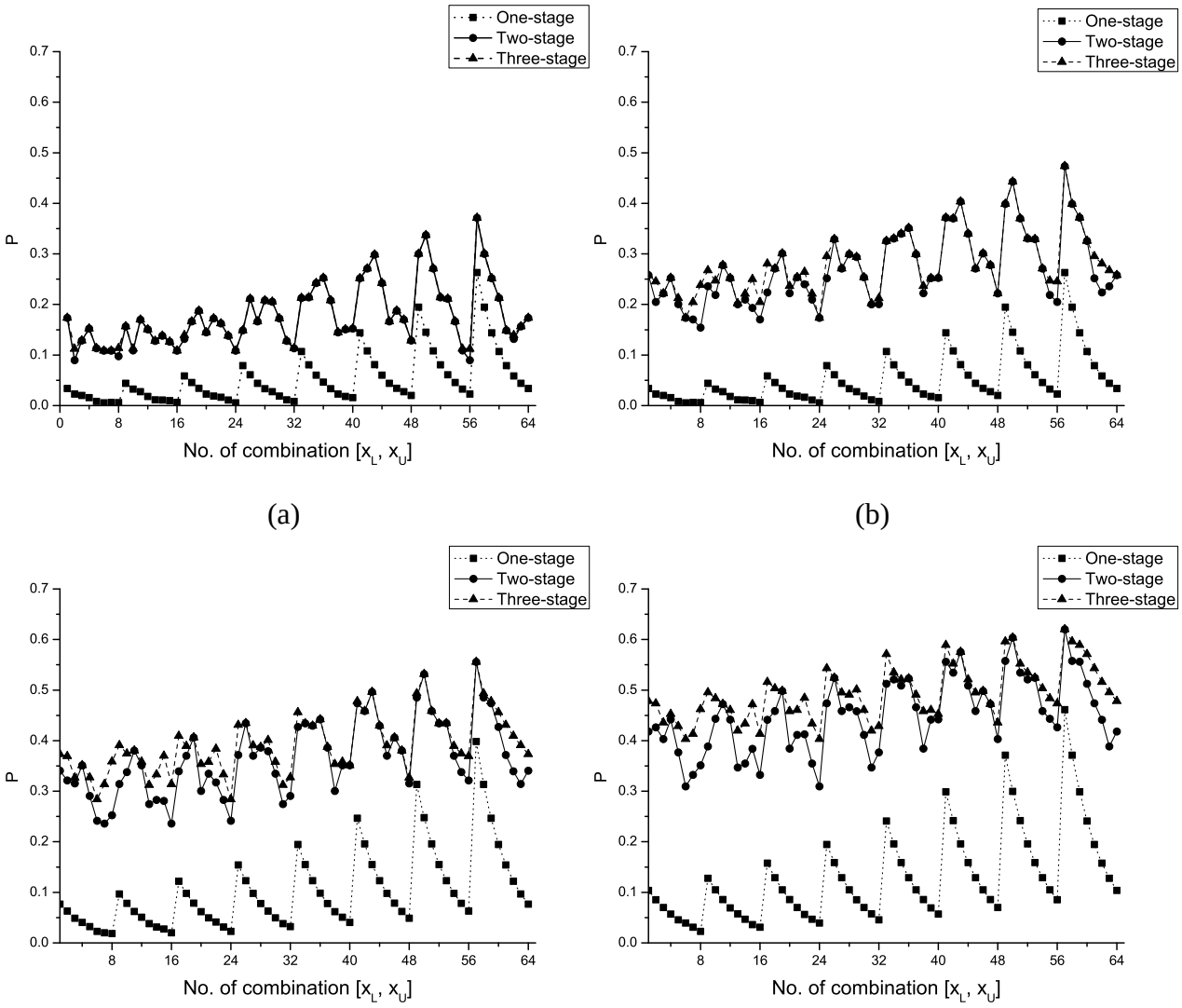

Figure 1: *Probabilities of achieving an overlap between three uniform designs. The total sample sizes for (a)-(d) are 6, 7, 8 and 9.*

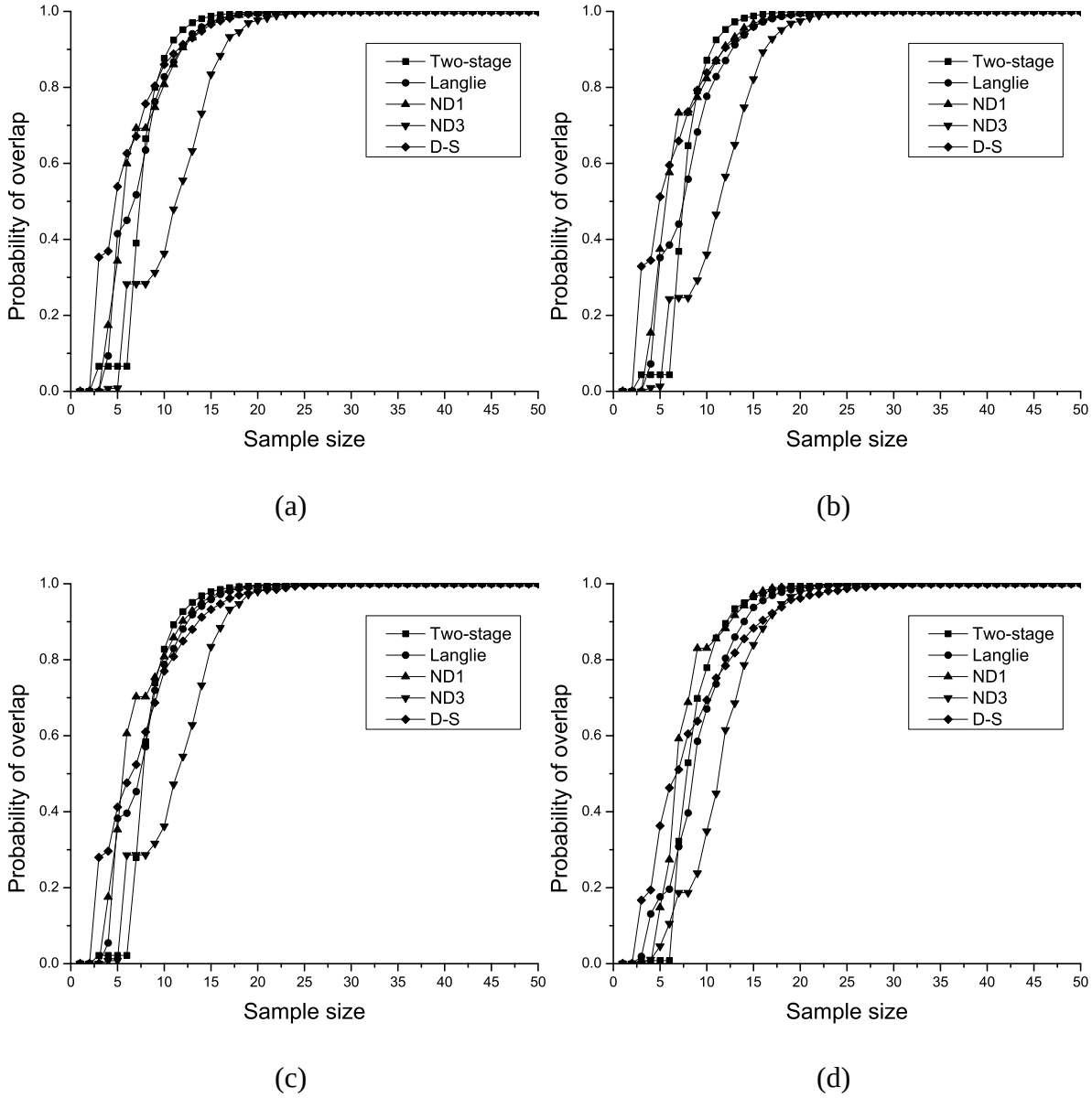

Figure 2: Comparison of probabilities of achieving an overlap for different choices of $[x_L, x_U]$: (a) $[-3, 3]$, (b) $[-3, 4]$, (c) $[-4, 4]$ and (d) $[-4, 7]$.