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Modified Turning Point Method for Confidence Interval Estimating on Up-And-Down Data. Application in Pharmacodynamic Research

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Abstract. The standard method of dealing with sensitive data is developed by Bliss and Fisher. The up-and-down method is one of the most important methods in sensitive experiments. Originated in an explosion experiment in Bruceton, Pennsylvania, in 1940, it is widely used in military and pharmaceutical research since then. Here we introduce a modified function based on the Choi turning point estimation [11] and compare it with three estimations — viz. with Dixon-Mood method, logistic regression, and isotonic regression. In order to estimate the confidence interval of ED50, we also developed an *R* package `ed50simulation` and employed it in pharmacodynamic research.

AMS subject classifications: 62P10, 62L12

Key words: Up-and-down method, confidence interval, 50% effective dose, modified turning point method, pharmacodynamic research.

1. Introduction

Dixon and Mood [6] introduced the up-and-down method (UDM) in order to estimate critical values in sensitive experiments based on dose tolerance distribution. Nowadays this simple method in widely used in pharmaceutical research such as measuring of 50% effective dose (ED50) and the minimum alveolar concentration of volatile anesthetics [11, 12]. Thus experiment starts with an initial dose and a fixed step size and its result determines the next test dose. More exactly, one passes to a higher dose level by adding one step size in the case of no response or decreases the dose by subtracting one step size in the case of

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success. Both the design of UDM and the statistical methods impact the accuracy of ED50 and CIs estimation [12].

UDM has many advantages — e.g. fast convergence of the tested value to its expectation even for small sample sets, say from 20 to 40 samples [11]. Besides, in order to achieve a required accuracy of ED50 estimation, the method needs fewer experiments because the experimental doses always do a small amount of shaking near the target true value starting from a certain experiment. Nevertheless, although there are additional requirements and assumptions such as nonrecurrent use of each subject in the same experiment, conducting of 40-50 trials for normally distributed variate of interest, the estimation results are quite acceptable — cf. [11].

There are several methods to estimate ED50 and the confidence interval (CI) for UDM data. One of them — viz. the turning point estimator, proposed by Wetherill [14] and modified by Choi [2], exploits only the peaks and troughs of the response series. The Choi's turning points estimator is easily applicable and has robustness of CI estimation. Therefore, it has been frequently used in anesthesia research [5,7,8,11–13]. The CI estimation based on the Choi's turning point method [3] has a number of potential advantages. The equality of ED50s in separated UDM studies can be assessed at a prespecified level based on the (non-)overlap of CIs [10]. Using the Choi's method, we calculated ED50 and 95% CIs for previously published data and the simulation results and discovered that 95% CIs are not consistent with the ones in the Choi's paper. By carefully repeating the derivation process, we demonstrate that the Choi's principle for CI estimation is reasonable. However, the Choi's functions for CI estimation are not valid without the centralisation process. Therefore, in order to estimate CIs of ED50, we modified the turning point method by centralising the turning point data and obtained good estimation results.

We also compare this modified turning point method with the most widely used parametric estimator — viz. the logistic regression, and with two non-parametric estimators — viz. Dixon and Mood estimator and isotonic regression. It was discovered that for different methods the convergence is sensitive to step size, so that the step size used in UDM should be chosen differently. If the step size is too small or too large, a very large sample set can be required for convergence. For each of the four estimators mentioned, an optimal step size is determined. It turns out that for the optimal step size, the estimation converges only in 15 to 25 turning points. Using the simulation results, we discuss how to choose a suitable estimator in practical experiments and how to design experiments with proper parameters.

The rest of the paper is organised as follow. In Section 2 we introduce the turning point method and present its correction with centralisation. Section 3 describes other three methods of interest. Simulations and the results analysis are presented in Section 4, and two groups of data from real experiments are processed in Section 5. Some discussion is given in Section 6, and our conclusion is in Section 7.

2. Modified Turning Point Method

The turning point method was proposed by Wetherill [14] in 1963 and modified by Choi [2] in 1971. Later on, Choi [3] provided functions for the estimation of ED50 and