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The Algorithm of Simulation and Justification of the Use of Conditional Likelihood in Up-and-Down Method

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Abstract

It should be noted that the number of observation in the up-and-down procedure is a random variable. Therefore, We need to justify the employment of the conditional likelihood even in the above situation and show the algorithm of simulation. Also, the strategy of halving or widening the level space in modified up-and-down method is suggested.

1. Introduction

The up-and-down method for estimating the LD50 of a quantal response curve is performed using a series of equally spaced test (dose) levels throughout the experiment: the first trial is performed at some dose level which may be nearest to the true LD50 and the subsequent trials are carried out sequentially without changing the spaces. In particular, each subsequent trial is performed at the next lower or the next higher dose level according to whether the immediately preceding trial did or did not evoke a response. This will be called an original up-and-down method and is shown in Figure 1.

The modification of the up-and-down technique is as follows: the first stage consists of an original up-and-down experiment on the predetermined equally spaced levels until k changes of response type are observed. The second stage consists of halving the initial space and restarting the sequence at the nearest level to the average based on the results up to that point and continuing the experiment at the next higher or the next lower space according to the response type on the new changed space. This idea was originally proposed by Wetherill et al. (1966). A typical process of the modification of the up-and-down method might look like Figure 1 where "x" and "0"denote the response (e.g., death) and non-response (e.g, survival), respectively.

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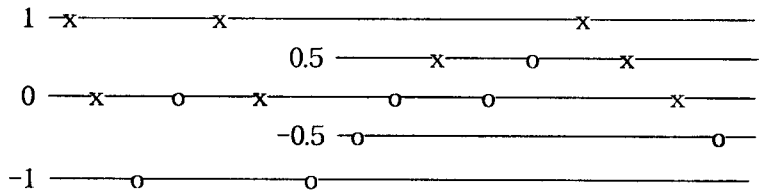


Figure 1. Example of modified up-and-down proces

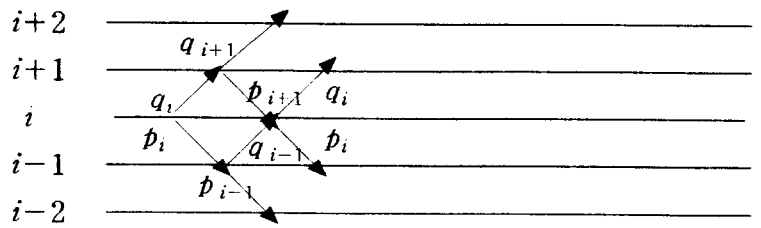
2. The Expected Number of Changes of Responses for Modified Up-and-Down Method

For the strategy of halving or widening the level space, we must consider the expected number of changes of responses for a given number of observations in the first stage conditioned on μ,σ and x_0. For example, if the observed number of changes is much greater than the expected number of changes then that would imply the space is too wide.

Let p_i denote the probability of response at the i^{th} dose level and assume that the number of dose levels is chosen so that $p_{-k}=0$, $p_k=1$, and $p_{-k}<p_{-k+1}\ldots<p_k$.

The series of experiments used in the up-and-down method form a one-dimensional random walk which is a Markov chain whose state space is a finite subset $-k,-k+1,\ldots,k$ of the integers in which the particle, if it is in stage i, can in a single transition move to one of the neighboring states, $i-1, i+1$. When i equals to state $-k$ *or* k, however, it can only move to state $-k+1$ or state $k-1$, respectively.

The one-dimensional random walk in up-and-down form can be depicted as in Figure 2.



p_i = probability of response at dose level i

q_i = probability of nonresponse at dose level i

Figure 2. One dimensional random walk in up-and-down process

The transition matrix A is expressed as

$$A = \begin{array}{c} \\ k \\ k-1 \\ k-2 \\ \vdots \\ \vdots \\ -k+1 \\ -k \end{array} \begin{array}{c} \begin{array}{cccccccccc} k & k-1 & k-2 & k-3 & k-4 & \cdots & -k+2 & -k+1 & -k \end{array} \\ \left[\begin{array}{cccccccccc} 0 & p_k & 0 & 0 & 0 & \cdots & 0 & 0 & 0 \\ q_{k-1} & 0 & p_{k-1} & 0 & 0 & \cdots & 0 & 0 & 0 \\ 0 & q_{k-2} & 0 & p_{k-2} & 0 & \cdots & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & 0 & \cdots & 0 & 0 & p_{-k+1} \\ 0 & 0 & 0 & 0 & 0 & \cdots & 0 & q_{-k} & 0 \end{array}\right] \end{array}$$

The expected number of changes of responses for n observations starting from i is

$$\sum_{j=-k}^{k} \sum_{h=1}^{l} c_{ijh} f_{ijh}^{(n-1)},$$

where $f_{ijh}^{(n-1)}$ denotes the h^{th} multiplication in the i^{th} row and j^{th} column element of matrix $A^{(n-1)}$, $\Sigma_{h=1}^{l} f_{ijh}^{(n-1)}$ denotes the probability of arriving at dose level j starting from dose level i at the n^{th} experiment, and c^{ijh} denotes the number of changes in responses of the h^{th} multiplication in the i^{th} row and j^{th} column element of matrix $A^{(n-1)}$.

As an example, if k=2 and n=3, the transition matrix can be

$$\begin{bmatrix} 0 & p_2 & 0 & 0 & 0 \\ q_1 & 0 & p_1 & 0 & 0 \\ 0 & q_0 & 0 & p_0 & 0 \\ 0 & 0 & q_1 & 0 & p_1 \\ 0 & 0 & 0 & q_2 & 0 \end{bmatrix} \begin{bmatrix} 0 & p_2 & 0 & 0 & 0 \\ q_1 & 0 & p_1 & 0 & 0 \\ 0 & q_0 & 0 & p_0 & 0 \\ 0 & 0 & q_1 & 0 & p_1 \\ 0 & 0 & 0 & q_2 & 0 \end{bmatrix}$$

$$= \begin{array}{c} \\ 2 \\ 1 \\ 0 \\ -1 \\ -2 \end{array} \begin{array}{c} \begin{array}{ccccc} 2 & 1 & 0 & -1 & -2 \end{array} \\ \left[\begin{array}{ccccc} p_2 q_1 & 0 & p_2 p_1 & 0 & 0 \\ 0 & q_1 p_2 + p_1 q_0 & 0 & p_1 p_0 & 0 \\ q_0 q_1 & 0 & q_0 p_1 + p_0 q_{-1} & 0 & p_0 p_{-1} \\ 0 & q_{-1} q_0 & 0 & q_{-1} p_0 + p_{-1} q_{-2} & 0 \\ 0 & 0 & q_{-2} q_{-1} & 0 & q_{-2} p_{-1} \end{array}\right] \end{array}$$

$$= f^{(3-1)}$$

The expected number of changes of responses for 3 experiments starting from dose level 1 can be

$$0 + 1(q_1 p_2) + 1(p_1 q_0) + 0 + 0(p_1 p_0) + 0 = q_1 p_2 + p_1 q_0$$

The expected number of cnanges of responses, assuming that $p_2 = 1$ and $q_{-2} = 1$ with

$k=2$, is shown in Table 1.

Table 1. The expected number of changes of responses

Interval	0.5	1		2		3	
Observation	6	6	10	6	10	6	10
Initial dose 0	2.49	2.90	5.52	3.26	6.19	3.33	6.32
1	2.10	2.63	5.32	2.93	5.88	3.00	6.00
2	1.19	2.05	4.67	2.00	4.93	2.00	5.00

As the initial dose increases and the interval decreases, the number of changes in responses tends to decrease, and vice versa.

3. Algorithm of Simulation in Up-and-Down Method

For quantal response data, the probability of response is commonly based on the concept of a tolerance distribution. The population of tolerance levels is assumed to be normally distributed with mean μ and variance σ^2. Let y_i be the log transformed tolerance level for i^{th} animal. Then we can write

$$x_i=\frac{y_i-\mu}{\sigma}=\beta_0+\beta_1 y_i \sim N(0,1).$$

Thus, μ and σ can be expressed as $-\beta_0/\beta_1$ and $1/\beta_1$, respectively. Assume tests are made at

$$y_i=y_0 \pm id, \quad i=1,2,\ldots,N,$$

where y_0 is the initial dose level and d is the equal distance between two successive dose levels. Let the number of response and non-responses at y_i be n_i and m_i, respectively.

The estimation of β_0 and β_1 is based on the principle of maximum likelihood.

Let p_i denote the probability of response at dose level i;

$$p_i=\int_{-\infty}^{y_i}\frac{1}{\sqrt{2\pi}}e^{\frac{(-\beta_0+\beta_1 t)^2}{2\sigma^2}}dt.$$

Let $q_i=1-p_i$. The distribution of these variates is given by

$$L(n,m,;\beta_0,\beta_1|y_0)=K\prod_{i=1}^{J}p_i^{n_i}q_i^{m_i}, \tag{1}$$

where K is not a function of β_0 and β_1 and J is the number of levels.

In formulating the likelihood function in an up-and-down method, it is noted that the number of observations, n_i+m_i, is a random variable. Thus, in a strict sense, the likelihood function is a conditional one. However, other authors including Dixon and Mood (1948) and Wetherill and Grazebrook (1986, p 186 - 187) also used the conditional likelihood function in a similar situation to estimate the parameters. Further, the simulation results presented by these authors indicated that the approach is satisfactory.

Therefore, we will employ the conditional likelihood given by (1) for estimating β_0 and β_1 and in the next section consider an unconditional likelihood.

Since closed-form expressions for the maximum likelihood estimates of β_0 and β_1 do not appear to exist, iterative solutions should be obtained. The initial estimates of maximum likelihood estimates can be obtained by the Spearman-Karber estimates which are asymptotically equivalent (Cornfield & Mantel, 1950) and the Spearman-Karber estimates are easily obtained. Let $\underline{\beta}^0$ denote initial estimates. We obtain the Spearman-Karber estimates as follows: The initial estimates are expressed as mean and variance. The estimated mean $\hat{\mu}$ is

$$\hat{\mu}^0 = \sum_{i=a+1}^{b} (\hat{p}_i - \hat{p}_{i-1})\left(\frac{x_i+x_{i-1}}{2}\right),$$

where a and b are the lowest and the highest level, respectively and $\hat{p}_i$ is the proportion of responses at level i. Also, the estimated variance, $\hat{\sigma}^{0^2}$ is given by

$$\hat{\sigma}^{0^2} = \sum_{i=a+1}^{b} (\hat{p}_i - \hat{p}_{i-1})\left(\frac{x_i+x_{i-1}}{2} - \hat{\mu}\right)^2 - k,$$

where k is Sheppard's correction (Cornfield, 1950) given by

$$k = \frac{\sum_{i=a+1}^{b} (\hat{p}_i - \hat{p}_{i-1})(x_i - x_{i-1})^2}{12}.$$

Since $\hat{\mu} = -\hat{\beta}_0/\hat{\beta}_1$ and $\hat{\sigma}^2 = 1/\hat{\beta}_1^2$, the initial estimates, β_0^0 and β_1^0, are $\beta_0^0 = -\hat{\mu}^0/\hat{\sigma}^0$ and $\beta_1^0 = 1/\hat{\sigma}^0$.

For the iterative solution, the Levenberg-Marquardt method, which is the modification of the Gauss-Newton algorithm first suggested by Levenberg (1944) and Marquardt (1963), is used. The algorithm we used is to choose β_+ by the trust region approach:

$$\textit{minimize}_{\beta_+ \in R^2} \| R(\underline{\beta}_c) + J(\underline{\beta}_c)(\underline{\beta}_+ - \underline{\beta}_c) \|_2 \qquad (2)$$

$$\textit{subject to} \| \underline{\beta}_+ - \underline{\beta}_c \|_2 \leq \delta_c,$$

where the residual matrix, $R(\underline{\beta}_c)$ is

$$R(\underline{\beta}_c) = \frac{\partial \log L}{\partial \underline{\beta}}\Big|_{\underline{\beta}=\underline{\beta}_c} - \underline{0}$$

$$= \left(\frac{\partial \log L}{\partial \beta_0} \quad \frac{\partial \log L}{\partial \beta_1}\right)_{\underline{\beta}=\underline{\beta}_c}.$$

$\underline{\beta}_c$ is the current value at evaluation, and the Jacobian matrix, the first derivative matrix of $R(\underline{\beta}_c)$, $J(\underline{\beta}_c)$ is

$$J(\underline{\beta}_c) = \begin{pmatrix} \frac{\partial^2 \log L}{\partial \beta_0^2} & \frac{\partial^2 \log L}{\partial \beta_0 \partial \beta_1} \\ \frac{\partial^2 \log L}{\partial \beta_0 \partial \beta_1} & \frac{\partial^2 \log L}{\partial \beta_1^2} \end{pmatrix} (\underline{\beta} = \underline{\beta}_c)$$

The solution to equation (2) is

$$\underline{\beta}_+ = \underline{\beta}_c - (J(\underline{\beta}_c)'J(\underline{\beta}_c) + \lambda_c I)^{-1} J(\underline{\beta}_c)' R(\underline{\beta}_c).$$

For the first $\underline{\beta}_c$, $\underline{\beta}^0$ can be used, where

$$\lambda_c = 0 \text{ if } \delta_c \geq \| (J(\underline{\beta}_c)'J(\underline{\beta}_c))^{-1} J(\underline{\beta}_c)' R(\underline{\beta}_c) \|_2$$

and $\lambda_c > 0$ otherwise. Value of λ_c and δ_c are chosen by the technique of the model trust region approach.

The estimate of LD_{50}, say $\hat{\mu}$, is

$$\hat{\mu} = -\hat{\beta}_0 / \hat{\beta}_1,$$

where $\hat{\underline{\beta}}$ is the maximum likelihood estimate by the Levenberg-Marquardt method.

The variance of $\hat{\mu}$ can be obtained by the delta method a

$$Var(\hat{\mu}) = \left(\frac{\partial \hat{\mu}}{\partial \beta_0} \quad \frac{\partial \hat{\mu}}{\partial \beta_1}\right) var(\hat{\underline{\beta}}) \left(\frac{\partial \hat{\mu}}{\partial \beta_0} \quad \frac{\partial \hat{\mu}}{\partial \beta_1}\right),$$

$$= \left(-\frac{1}{\hat{\beta}_1} \quad \frac{\hat{\beta}_0}{\hat{\beta}_1^2}\right) I^{-1}(\hat{\underline{\beta}}) \left(-\frac{1}{\hat{\beta}_1} \quad \frac{\hat{\beta}_0}{\hat{\beta}_1^2}\right),$$

where

$$I^{-1}(\hat{\underline{\beta}_c}) = \begin{pmatrix} -\frac{\partial^2 \log L}{\partial \beta_0^2} & -\frac{\partial^2 \log L}{\partial \beta_0 \partial \beta_1} \\ -\frac{\partial^2 \log L}{\partial \beta_0 \partial \beta_1} & -\frac{\partial^2 \log L}{\partial \beta_1^2} \end{pmatrix}^{-1} (\underline{\beta} = \underline{\beta}_c).$$

Therefore, the large sample 100(1-α)% confidence interval is

$$\hat{\mu} \pm z_{\alpha/2}\sqrt{var(\hat{\mu})}.$$

4. Justification of the Use of the Conditional Likelihood

Once again, it should be noted that the number of observation in the up-and-down procedure is a random variable. Therefore, in order to employ the conditional likelihood (1), the number of observations at each dose level is assumed fixed. Wetherill and Glazebrook (1986, p.186) derived the asymptotic distribution of the observations at the fixed series of dose levels. We used the asymptotic number of observations as NP_i instead of the empirical number of observations and constructed the unconditional likelihood. In this section, we shall consider two cases depending on i which represents the dose level.

The distribution is given by

$$L(n, P_0, N, \beta_0, \beta_1 | y_0) = \begin{cases} K \prod_{i=1}^{T^+} p_i^{n_i} (1-p_i)^{NP_i - n_i} & \text{if } i \geq 1 \\ K \prod_{i=T^-}^{-1} p_i^{n_i} (1-p_i)^{NP_i - n_i} & \text{if } i \leq -1, \end{cases} \tag{3}$$

where

$$P_i = \begin{cases} P_0 \prod_{k=0}^{i-1} (1-p_k) \Big/ \prod_{j=1}^{i} p_j & \text{if } i \geq 1 \\ P_0 \prod_{j=i+1}^{0} p_j \Big/ \prod_{k=i}^{-1} (1-p_k) & \text{if } i \leq -1, \end{cases}$$

$T^+ =$ the highest testing dose level when $i \geq 1$,

and $T^- =$ the lowest testing dose level when $i \leq -1$.

By taking the first derivative of the log likelihood function of (3) with respect to β_0 and β_1, respectively, we get

$$\frac{\partial \log L}{\partial \beta_0} = \begin{cases} \sum_{i=1}^{T^+} \left[\frac{n_i f_i}{p_i} - \frac{NP_i \log(1-p_i)}{p_i} - \frac{NP_i f_i - n_i f_i}{1-p_i} \right] & i \geq 1 \\ \sum_{i=T^-}^{-1} \left[\frac{n_i f_i}{p_i} - \frac{NP_i f_i (\log(1-p_i) - 1) + n_i f_i}{1-p_i} \right] & i \leq -1, \end{cases}$$

$$\frac{\partial \log L}{\partial \beta_1} = \begin{cases} \sum_{i=1}^{T^+} \left[\frac{n_i y_i f_i}{p_i} - \frac{NP_i y_i f_i \log(1-p_i)}{p_i} - \frac{NP_i y_i f_i - n_i y_i f_i}{1-p_i} \right] & i \geq 1 \\ \sum_{i=T^-}^{-1} \left[\frac{n_i y_i f_i}{p_i} - \frac{NP_i y_i f_i \log(1-p_i) - y_i f_i + n_i y_i f_i}{1-p_i} \right] & i \leq -1. \end{cases}$$

In both cases, the Levenberg-Marquardt method is used to obatin the maximum likelihood estimates of β_0 and β_1.

In oder to compare the m.l.e of the conditional likelihood, we choose two designs of original up-and-down method for simulation.The standard normal distribution is assumed as the tolerance distribution for comparing the above two likelihoods. For the initial doses, we used 0 and 1σ for the simulation with 1σ and 0.5σ as the interval between two successive dose levels. Each experimental design is simulated 500 times; the averages of $\hat{\beta}_0$, $\hat{\beta}_1$, and $\hat{\mu}$ are obtained in each of 5 groups of 100 simulations and their standard errors are obtained. For example, the standard error of $\hat{\beta}_0$ is

$$\text{S.E.}(\hat{\beta}_0) = \sqrt{\sum_{i=1}^{5} \frac{(\bar{\beta}_{0i} - \bar{\beta}_0)^2}{4}},$$

where $\bar{\beta}_{0i}$ is the average of $\hat{\beta}_0$ for the i^{th} group and $\bar{\beta}_0$ is the mean of 500 simulations.

Tables 2 and 3 show the results of the simulation study when the true values are $\beta_0 = 0, \beta_1 = 1$, and $\mu = 0$. In general, there is no difference between the two likelihoods over sample sizes 20 to 150 according to the mean of $\hat{\beta}_0$, $\hat{\beta}_1$, $\hat{\mu}$, and M.S.E. $(\hat{\mu})$. Therefore, we can justify the use of the conditional likelihood (1) because the conditional likelihood is more practical to obtain the parameter estimates than the unconditional likelihood (3).

Table 2. Simulation results

Initial dose = 0σ and Interval = 1σ

Sample Size	20		30		50		150	
Likelihood	Cond	Uncond	Cond	Uncond	Cond	Uncond	Cond	Uncond
Mean ($\hat{\beta}_0$)	.000	-.007	-.005	-.018	-.014	-.020	-.015	-.025
S.E.($\hat{\beta}_0$)	.157	.165	.076	.081	.054	.052	.019	.019
Mean ($\hat{\beta}_1$)	1.674	1.619	1.405	1.448	1.210	1.266	1.062	1.105
S.E. ($\hat{\beta}_1$)	.476	.099	.150	.108	.103	.079	.040	.052
Mean ($\hat{\mu}$)	.004	.008	.003	.010	.012	.015	.015	.023
S.E. ($\hat{\mu}$)	.093	.095	.042	.043	.045	.042	.020	.019
M.S.E. ($\hat{\mu}$)	.114	.115	.070	.070	.037	.041	.014	.017

Table 3. Simulation results

Initial dose = 1σ and Interval=0.5σ

Sample Size	20		30		50		150	
Likelihood	Cond	Uncond	Cond	Uncond	Cond	Uncond	Cond	Uncond
Mean ($\hat{\beta}_0$)	-.138	-.169	-.134	-.094	-.048	-.061	-.026	-.039
S.E.($\hat{\beta}_0$)	.200	.198	.156	.081	.045	.047	.419	.031
Mean ($\hat{\beta}_1$)	2.066	2.080	1.901	1.597	1.367	1.431	1.068	1.172
S.E. ($\hat{\beta}_1$)	.481	.422	.421	.147	.139	.139	.221	.040
Mean ($\hat{\mu}$)	.041	.066	.019	.061	.028	.039	.003	.034
S.E. ($\hat{\mu}$)	.082	.078	.100	.047	.023	.028	.036	.031
M.S.E. ($\hat{\mu}$)	.120	.108	.089	.079	.063	.063	.065	.061

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