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ASYMPTOTIC PROPERTIES OF $\bar{w}$, AN ESTIMATOR OF THE ED50 SUGGESTED FOR USE IN UP-AND-DOWN EXPERIMENTS IN BIO-ASSAY

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Wetherill's estimator $\bar{w}$ is asymptotically equivalent to the mean of peaks and valleys in the sequence of responses in an up-and-down experiment. The asymptotic distribution of $\bar{w}$ is derived and the asymptotic variance expression is simplified. Some values of asymptotic means and variances are calculated for logistic response. They are compared with analogous values for the estimator suggested by Dixon and Mood. These estimators are also compared by some computer simulation. For the conditions investigated, Dixon and Mood's estimator is to be preferred to $\bar{w}$.

1. Introduction. In the up-and-down method binary response observations are made sequentially. The rule followed is that if the response at the current level is positive then the next observation is made at some fixed distance d below this level, otherwise it is made at d above. This method has been used in bio-assay where it is assumed that the probability of positive response increases monotonically with stimulus level. Some of the earliest references to this method are in Dixon and Mood (1948) and Brownlee, Hodges and Rosenblatt (1953). They suggest that one should use, as approximate estimators for the ED50, estimators which are asymptotically equivalent to the mean of the levels visited (in the following this is referred to as the mean level estimator).

Tsutakawa (1967a) gives conditions under which such estimators are asymptotically normally distributed and derives expressions for the asymptotic mean and variance of these estimators. Wetherill (1966) and Wetherill, Chen and Vasudeva (1966) discuss another estimator $\bar{w}$. They say that an intuitive estimator of the ED50 is the level midway between any two consecutive levels visited for which responses are of opposite sign. The estimator $\bar{w}$ is just the unweighted mean of all such estimates from an experiment. This estimator is asymptotically equivalent to the mean of the peaks and valleys in the sequence of levels visited (see Choi, 1971), where a peak is defined as a level reached from below at which there is a positive response, and a valley is a level reached from above at which there is a negative response. To find the asymptotic expectation of this estimator, Wetherill et al. suggest that one should view the process as a Markov chain of alternating peaks and valleys. They make a finite Markov chain approximation to the process and then find approximations to the equilibrium probabilities for the states by calculating eigen vectors for two matrices. They remark that the matrices are often ill conditioned and that it is difficult to obtain accurate eigen

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vectors. Choi also adopts this approach and in an appendix finds an expression for the variance of $\bar{w}$ in small samples. These papers do not give an expression for the asymptotic variance of $\bar{w}$. Theorems 1 and 2 in Section 2 obtain asymptotic expressions for the expectation and variance of $\bar{w}$, and in Section 3 the asymptotic variance expression is simplified.

2. The asymptotic distribution of $\bar{w}$. In the following the response curve is assumed to be monotonic increasing, and to take values above and below ½. Suppose the starting level in an up-and-down experiment is x_0. The stimulus levels that can be visited are x_i, for some integer i, where

$$x_i = x_0 + id. \tag{2.1}$$

Suppose the probability of positive response at x_i is F_i. The sequence of levels visited in operating the up-and-down rule can be thought of as states visited in a Markov chain with transition probabilities of moving from x_i to x_{i+1} or x_{i-1} being $1 - F_i$ and F_i respectively. Under the conditions that have been assumed, it is easy to show that the states form a positive class with some equilibrium distribution $\{\Pi_i\}$, where the Π_i satisfy the equation of the form

$$\Pi_i(1 - F_i) = \Pi_{i+1}F_{i+1}. \tag{2.2}$$

Tsutakawa's method to find the asymptotic distribution of the mean of the levels visited is to regard the sum of the levels visited as a functional on this Markov chain. In deriving the asymptotic distribution for $\bar{w}$, it is useful to consider the following Markov chain in which the state of being at level x_i is further subdivided into states (x_i, θ), where $\theta = 1, 2, 3$ or 4. State $(x_i, 1)$ is entered when level x_i is reached from x_{i-1} and the level two steps before was x_i, $(x_i, 2)$ is entered if instead this level was x_{i-2}. State $(x_i, 3)$ is entered when level x_i is reached from x_{i+1} and the level two steps before was x_i; $(x_i, 4)$ is entered if instead this level was x_{i+2}. The equilibrium probability of being in state (x_i, θ) will be denoted by $\pi_{i\theta}$. From states $(x_i, 1)$ and $(x_i, 2)$, one moves at the next step to states $(x_{i-1}, 3)$ or $(x_{i+1}, 2)$ with probabilities F_i and $(1 - F_i)$; from states $(x_i, 3)$ and $(x_i, 4)$, one moves at the next step to states $(x_{i-1}, 4)$ or $(x_{i+1}, 1)$ again with probabilities F_i and $(1 - F_i)$. For all of these states the level visited two steps previously is known. Expression for the $\pi_{i\theta}$ in terms of the Π_i can be easily derived. To reach state $(x_i, 1)$ one must be at level x_i two steps before and take a step down followed by a step up. The equilibrium probability of being at x_i is Π_i and there is probability of moving into state $(x_i, 1)$ after two steps of $F_i(1 - F_{i-1})$, so π_{i1} is given by

$$\pi_{i1} = F_i(1 - F_{i-1})\Pi_i. \tag{2.3}$$

By similar arguments π_{12}, π_{i3} and π_{i4} are given by

$$\pi_{i2} = (1 - F_{i-2})(1 - F_{i-1})\Pi_{i-2}, \tag{2.4}$$

$$\pi_{i3} = (1 - F_i)F_{i+1}\Pi_i, \tag{2.5}$$

$$\pi_{i4} = F_{i+2}F_{i+1}\Pi_{i+2}. \tag{2.6}$$

State $(x_{i+1,1})$ is reached if and only if one has just arrived at x_{i+1} from a valley of x_i; state $(x_{i-1,3})$ is reached if and only if one has just arrived at x_{i-1} from a peak at x_i. Wetherill et al. derived equations for equilibrium probabilities for the Markov chain of alternating peaks and valleys. They tried to solve these equations by finding eigenvalues of matrices. If in their equations they had substituted the expressions for $\pi_{i+1,1}$ and $\pi_{i-1,3}$ for the equilibrium probabilities for valleys and peaks at x_i, they would have found after a short amount of calculation that these values are proportional to the unique solutions of the equations.

Define

$$g(x_i, \theta) = x_i - p \quad \text{if} \quad \theta = 1 \quad \text{or} \quad 3, \tag{2.7}$$

$$g(x_i, \theta) = 0 \qquad \text{if} \quad \theta = 2 \quad \text{or} \quad 4, \tag{2.8}$$

where

$$p = \textstyle\sum_{j,\theta=1,3} \pi_{j\theta} x_j / \sum_{j,\theta=1,3} \pi_{j\theta}. \tag{2.9}$$

Suppose that (y_T, θ_T), for $T = 1, \cdots, n$, are the first n states visited in this Markov chain (here $n + 1$ observations are made; y_T equals the level that would be moved to following $T + 1$ observations). In Theorem 1 the asymptotic distribution of the mean of the values of $g(y_T, \theta_T)$ is derived. In Theorem 2 this result is used to derive the asymptotic distribution of $\bar{w}$ and it is shown that p is the asymptotic expectation of $\bar{w}$.

THEOREM 1. *$\sum_{T=1}^{n} g(y_T, \theta_T)/n$ has an asymptotic $N(0, U/n)$ distribution, where*

$$\begin{aligned} U = {} & \textstyle\sum_{j,\theta} \pi_{j\theta} g(x_j, \theta)^2 \\ & + 2 \textstyle\sum_{j,\theta} \pi_{j\theta} g(x_j, \theta) \sum_{(k,\phi)\neq(i,\theta_0)} \pi_{k\phi} g(x_k, \phi) v(j, \theta, k, \phi) \end{aligned} \tag{2.10}$$

and

$$v(j, \theta, k, \phi) = M(j, \theta, i, \theta_0) + M(i, \theta_0, k, \phi) - M(j, \theta, k, \phi) \tag{2.11}$$

and $M(j, \theta, k, \phi)$ is the mean first passage time from state (x_j, θ) to (x_k, ϕ). Any (i, θ_0) such that (x_i, θ_0) is a possible state can be used in (2.10).

PROOF. This result follows from applying results in Chung (1966). The mean of the $g(y_T, \theta_T)$ is a functional on the Markov chain with states (i, θ).

Consider $\sum_{T=1}^{\tau-1} g(y_T, \theta_T)$, where τ is the time at which there is a first return to the initial state (y_1, θ_1). From Theorems 5 and 6 on page 87 of Chung it follows that this sum has expectation 0. Theorem 7 on page 88 of Chung gives an expression for the expected square of the sum. After using the identity $M_{j\theta,j\theta} = 1/\pi_{j\theta}$, one can deduce that this expectation equals $U/\pi_{i\theta}$. The asymptotic normality of the mean of the $g(y_T, \theta_T)$ follows on applying Theorem 1 on page 99 of Chung. For the result to hold, absolute convergence of terms in the summations is required. In Section 3 of this paper it is shown that for a monotonic increasing response curve taking value above and below ½, these sums are absolutely convergent.

THEOREM 2. *The estimator $\bar{w}$ has an asymptotic $N(p, U/q^2n)$ distribution where*

$$q = \sum_{j,\theta=1,3} \pi_{j\theta}. \tag{2.12}$$

PROOF. $\sum_{T=1}^{n} g(y_T, \theta_T)/n$ divided by the proportion of times $\theta_T = 1$ or 3, is

$$\left(\sum_j x_j(\lambda_{j+1} + \gamma_{j-1})/\sum_j(\lambda_j + \gamma_j)\right) - p, \tag{2.13}$$

where λ_j is the number of peaks at x_j and γ_j is the number of valleys. From Theorem 2 on page 92 of Chung it follows that

$$\text{Plim} \sum_j(\lambda_j + \gamma_j)/n = q, \tag{2.14}$$

where Plim denotes the limit with probability one. It follows that the expression in (2.13) has an asymptotic $N(0, U/q^2n)$ distribution.

From the definition of $\bar{w}$

$$\bar{w} = \sum_j (x_j + d/2)(\lambda_{j+1} + \gamma_j)/\sum_j (\lambda_j + \gamma_j). \tag{2.15}$$

The numbers of peaks and valleys differ by at most 1 so

$$\left| \sum_j (\lambda_j - \gamma_j) \right| = 1 \quad \text{or} \quad 0. \tag{2.16}$$

The difference between $\bar{w} - p$ and the expression in (2.13) is bounded in modulus by

$$d/2 \sum (\lambda_j + \gamma_j), \tag{2.17}$$

which tends in probability to 0. So $\bar{w} - p$ and the expression in (2.13) have the same asymptotic distribution, that is $\bar{w}$ also has a $N(p, U/q^2n)$ distribution.

The expression for U can be simplified; to do this one must express the $M(j, \theta, k, \phi)$ for θ and $\phi = 1$ or 3 in terms of m_{jk}, where m_{jk} is the mean first passage time from x_j to x_k.

3. Simplification of the asymptotic variance expression. Cases where (x_k, ϕ) can be reached from (x_j, θ) in a minimum of one, two or more than two steps will be considered separately.

CASE 1. *States reached in one step.* Starting in state $(x_j, 1)$ one can move in one step to $(x_{j-1}, 3)$ with probability F_j and to $(x_{j+1}, 2)$ with probability $1 - F_j$. If one moves into state $(x_{j+1}, 2)$, the expected further number of steps taken before reaching $(x_{j-1}, 3)$ is by definition $M(j + 1, 2, j - 1, 3)$, so

$$M(j, 1, j - 1, 3) = 1 + (1 - F_j)(M(j + 1, 2, j - 1, 3)). \tag{3.1}$$

By an exactly similar argument

$$M(j, 3, j + 1, 1) = 1 + F_j(M(j - 1, 4, j + 1, 3)). \tag{3.2}$$

In considering Case 3 (i.e. where a state can only be reached after more than two steps) expressions for $M(j+1, 2, j-2, 3)$ and $M(j-1, 4, j+1, 3)$ are derived.

CASE 2. *States reached in two steps.* Starting from state (x_j, θ) then, whatever the value of θ, it will take at least two steps to enter either state $(x_j, 1)$ or $(x_j, 3)$. The probability of moving to any state from (x_j, θ) after two steps is independent of θ, as θ only gives information about the two steps made before entering (x_j, θ). It follows that $M(j, \theta, j, 1)$ and $M(j, \theta\, j, 3)$ are independent of θ; that is

$$M(j, \theta, j, \phi) = M(j, \phi, j, \phi) \quad \text{for} \quad \phi = 1 \text{ or } 3. \tag{3.3}$$

CASE 3. *States reached in more than two steps.* Suppose $M(j, \theta, k, \phi)$ is required where $\phi = 1$ or 3. Suppose further that (x_k, ϕ) cannot be reached from (x_j, θ) in one step and also that $j \neq k$ (i.e. (x_k, ϕ) cannot be reached in two steps). Two steps previous to being in state (x_k, ϕ), one must be at level x_k, so one must pass through some state (x_k, β), where $\beta \neq \phi$, in the sequence of states visited in moving from (x_j, θ) to (x_k, ϕ). The first passage time consists of the first passage time from (x_j, θ) to any state (x_k, β) plus the first passage time from (x_k, β) to (x_k, ϕ). The first of these times is just a first passage time from x_j to x_k and has mean m_{jk}; from (3.3) the second has mean $M(k, \phi, k, \phi)$ so

$$M(j, \theta, k, \phi) = m_{jk} + M(k, \phi, k, \phi). \tag{3.4}$$

Formula (3.4) can be used within formulae (3.1) and (3.2), which gives

$$M(j, 1, j-1, 3) = m_{j,j-1} + (1 - F_j)(M(j-1, 3, j-1, 3)), \tag{3.5}$$

$$M(j, 3, j+1, 1) = m_{j,j+1} + F_j(M(j+1, 1, j+1, 1)). \tag{3.6}$$

Expressions (3.3) to (3.6) do simplify calculation of the $M(j, \theta, k, \phi)$ as the $M(k, \phi, k, \phi)$ terms are mean first return times to the states and so equal $1/\pi_{k\phi}$.

In the following the state (i, θ_0) used in (2.10) is set equal to (0, 1). When formula (3.3) and (3.4) apply throughout the expression in (2.9)

$$v(j, \theta, k, \phi) = M(0, 1, 0, 1) + z_{jk}, \tag{3.7}$$

where

$$z_{jk} = (1 - \delta_{j0})m_{j0} + (1 - \delta_{0k})m_{0k} - (1 - \delta_{jk})m_{jk}, \tag{3.8}$$

and δ_{jk} is the Kronecker delta. In general a correction will have to be made to the right-hand side in (3.7) whenever (3.5) or (3.6) have to be used in calculation. In the following, U is calculated under the assumption that (3.7) always holds and then the appropriate adjustment to this value is given.

The $M(0, 1, 0, 1)$ term when substituted into the expression (2.10) for U will vanish because $\sum_{j,\theta} \pi_{j\theta} g(x_j, \theta) = 0$. The expression for z_{jk} can be simplified

$$z_{jk} = \begin{cases} 0 & \text{if } j = 0 \text{ or } k = 0 \\ 0 & \text{if } j > 0 > k \text{ or } k > 0 > j \text{ because then } m_{j0} + m_{0k} = m_{jk} \\ m_{j0} + m_{0j} & \text{if } 0 < j < k \text{ or } 0 > j > k \text{ because then } m_{0j} + m_{jk} = m_{0k} \\ m_{k0} + m_{0k} & \text{if } 0 < k < j \text{ or } 0 > k > j \text{ because then } m_{jk} + m_{k0} = m_{j0} \\ m_{j0} + m_{0j} & \text{if } j = k \text{ but } j \neq 0. \end{cases}$$

So the contribution to U from this term is

$$\begin{aligned}(3.8)\qquad &\textstyle\sum_{j,\theta} \pi_{j\theta}g(x_j\theta)^2 + 4\sum_{0<j<k,k<j<0,\theta,\phi} \pi_{j\theta}\pi_{k\phi}g(x_j, \theta)g(x_k, \phi)(m_{j0} + m_{0j}) \\ &\qquad + 2\textstyle\sum_{j\neq 0,\theta,\phi} \pi_{j\theta}\pi_{j\phi}g(x_j, \theta)g(x_j, \phi)(m_{j0} + m_{0j}).\end{aligned}$$

Harris (1952) shows that for $i = 0$, $(m_{i0} + m_i) = 1/\Pi_i\rho_i$, where ρ_i is the probability that starting at x_i one reaches x_0 before returning to x_i. There exist recurrence relations for calculating the ρ_i (see Tsutakawa, 1967a).

The first term on the right-hand side of (2.11), when $(i, \theta_0) = (0, 1)$, must be calculated using (3.6) if $(j, \theta) = (-1, 3)$. The second must be calculated using (3.5) if $(k, \phi) = (-1, 3)$. The third must be calculated using (3.5) or (3.6) when one of the pair (j, θ) and (k, ϕ) takes, for some integer r, value $(r + 1, 1)$ and the other value $(r, 3)$. The adjustment to U due to the first term is

$$(3.10)\qquad -2\pi_{-1,3}(1 - F_{-1})M(0, 1, 0, 1)g(x_{-1}, 3) \textstyle\sum_{(j,\theta)\neq(0,1)} \pi_{j\theta}g(x_j, \theta).$$

As $\sum_{j,\theta} \pi_{j\theta}g(x_j, \theta) = 0$ the summation factor in (3.10) is $-\pi_{0,1}g(x_0, 1)$. The adjustment to U due to the second term vanishes because $\sum_{j,\theta} \pi_{j\theta}g(x_j, \theta)$ enters as a factor into the adjustment. The adjustment to U due to the third term is

$$\begin{aligned}(3.11)\qquad &2(\textstyle\sum_j \pi_{j1}\pi_{j-1,3}F_jM(j - 1, 3, j - 1, 3)g(x_j, 1)g(x_{j-1}, 3)) \\ &+ 2(\textstyle\sum_{j\neq -1} \pi_{j3}\pi_{j+1,1}(1 - F_j)M(j + 1, 1, j + 1, 1)g(x_{j+1}, 1)g(x_j, 3)).\end{aligned}$$

The term missing in the second summation in (3.11) is just the expression in (3.10). Simplifying, using the identity $M(j, \theta, j, \theta) = 1/\pi_{j\theta}$, it follows that the total adjustment is

$$(3.12)\qquad 2\textstyle\sum_j \pi_{j1}F_jg(x_j, 1)g(x_{j-1}, 3) + 2\sum_j \pi_{j3}(1 - F_j)g(x_{j+1}, 1)g(x_j, 3).$$

From (2.2), (2.3) and (2.5) it follows that $\pi_{j+1,1}F_{j+1} = \pi_{j3}(1 - F_j)$ and that (3.12) can be simplified to

$$(3.13)\qquad 4\textstyle\sum_j \Pi_jF_j^2(1 - F_{j-1})c_jc_{j-1},$$

where $c_j = x_j - p$. From Theorem 2 and using the expression (3.8) and (3.13) together with Harris' result, it follows that $\bar{w}$ has an asymptotic $N(p, U^*/n)$ distribution where

$$\begin{aligned}U^* = (&\textstyle\sum_j \Pi_jc_j^2w_j(1 + (2W_j/\rho_j) \\ &+ 4\textstyle\sum_{0<i<j,j<i<0} \Pi_jc_ic_jW_iW_j/\rho_i - 2\Pi_0c_0^2W_0^2 + 4\sum_j \pi_jc_jc_{j-1}Z_j))/q^2,\end{aligned}$$

and $W_j = (F_j(1 - F_{j-1}) + (1 - F_j)F_{j+1})$, $Z_j = F_j^2(1 - F_{j-1})$ and ρ_0 is defined as 1. (Note that $p = \sum_j \Pi_jW_jx_j/\sum_j \Pi_jW_j$ and $q = \sum_j \Pi_jW_j$).

Tsutakawa (1967a) shows that $\inf_i\rho_i > 0$. He also shows that the sum of $\Pi_j|x_j|^h$ over all j is convergent for any positive integer h. From these results it follows that all the summations that have been considered are absolutely convergent.

It is interesting to compare the expression in (3.14) with the analogous expression for the mean level estimator given in Tsutakawa (1967b). The c_j equal $x_j - p$; if throughout (3.14), p is replaced by $\sum \Pi_jx_j$, q by 1, W_j by -1 and Z_j by

0, then the resulting expression is the asymptotic variance expression for the mean level estimator. So a program for calculating the asymptotic variance of $\bar{w}$ can be easily adopted to calculate that of the mean level estimator.

4. Comparison of $\bar{w}$ and mean level estimator. The expressions for p and U^* are infinite sums, but the Π_i are decreasing to zero at least exponentially as $|i| \to \infty$. The values of p and U^* have been calculated for the case where the response curve is logistic, that is

$$F_i = 1/(1 + \exp(-\beta(x_i - \mu))). \tag{4.1}$$

In the calculations, the sums were truncated 40 steps above and below the level nearest to μ.

From symmetry the asymptotic biases for $\bar{w}$ for μ/d equal to x and $-x$ will, for all x, be of the same magnitude but opposite sign; the asymptotic variances will be equal. If μ/d equals $k + x$, for some integer k, then the asymptotic bias and variance will be the same as when μ/d equals x (the scale has been translated without the phasing of levels being altered). If one knows the bias and variance for $\mu/d \in [0, \frac{1}{2})$ then one can deduce the bias for all μ/d values. Table 1 gives calculated values of biases and variance of $\bar{w}$ for $\beta d = 0.25, 0.50, 1.00, 2.00, 3.00, 4.00$ and $\mu/d = 0.00, 0.10, 0.20, 0.25, 0.30, 0.40, 0.50$ (the biases for $\mu/d = 0.00$ and 0.50 are zero; this follows from the symmetry arguments). The remarks concerning biases and variances for $\bar{w}$ also apply to the mean level estimator. Table 2 gives calculated values for the mean level estimator, analogous to those in Table 1, of biases and variances.

The biases for both estimators are small when d is small. The asymptotic variance expressions for $\bar{w}$ are, for the small values of d, slightly above those for the mean level estimator, and much more dependent on the value of μ/d for large values of d. These calculations appear to contradict the evidence given by Wetherill (1966) and Wetherill et al. (1966) in that the mean level estimator appears to have some definite advantages over $\bar{w}$. They reported results of simulations where an estimator suggested by Brownlee et al. (1953) (which is

TABLE 1

Values of asymptotic bias/d and asymptotic variance $\times\ \beta^2 n$ for $\bar{w}$ (where n is the number of observations). Values of bias/d are 0.000 *to* 3 *decimals for* βd = 0.25, 0.50 *and* 1.00.

μ/d	βd 0.25	0.50	1.00	2.00		3.00		4.00	
	var $\beta^2 n$	var $\beta^2 n$	var $\beta^2 n$	bias/d	var $\beta^2 n$	bias/d	var $\beta^2 n$	bias/d	var $\beta^2 n$
0.500	4.428	4.769	5.356	0.000	6.202	0.000	5.836	0.000	4.660
0.400	4.428	4.769	5.356	0.002	6.258	0.015	6.174	0.034	5.313
0.300	4.428	4.769	5.356	0.004	6.407	0.025	7.111	0.056	7.314
0.250	4.428	4.769	5.357	0.004	6.499	0.026	7.731	0.061	8.798
0.200	4.428	4.769	5.357	0.004	6.592	0.025	8.384	0.059	10.508
0.100	4.428	4.769	5.357	0.002	6.744	0.016	9.514	0.038	13.852
0.000	4.428	4.769	5.357	0.000	6.802	0.000	9.972	0.000	15.353

TABLE 2

Values of asymptotic bias/d and asymptotic variance × $\beta^2 n$ *for* E_{DM}. *Values of bias/d are* 0.000 *to* 3 *decimals for* βd = 0.25, 0.50, 1.00 *and* 2.00.

μ/d	βd 0.25 var $\beta^2 n$	0.50 var $\beta^2 n$	1.00 var $\beta^3 n$	2.00 var $\beta^2 n$	3.00 bias/d	3.00 var $\beta^2 n$	4.00 bias/d	4.00 var $\beta^2 n$
0.500	4.253	4.514	5.056	6.220	0.000	7.324	0.000	7.879
0.400	4.253	4.514	5.056	6.221	0.003	7.361	0.013	8.078
0.300	4.253	4.514	5.056	6.224	0.006	7.458	0.021	8.606
0.250	4.253	4.514	5.056	6.225	0.006	7.518	0.023	8.941
0.200	4.253	4.514	5.056	6.270	0.006	7.518	0.022	9.281
0.100	4.253	4.514	5.056	6.230	0.003	7.677	0.013	9.845
0.000	4.253	4.514	5.056	6.231	0.000	7.714	0.000	10.065

TABLE 3

M.s.e.'s of E_{DM} *and* $\bar{w}$ *from* 96 *observation experiments, with* 2000 *simulations per set of conditions,* $\beta = \pi/\sqrt{3}$; *together with asymptotic predicted m.s.e.'s.*

Start	$d = 0.05$ 100 × m.s.e. of E_{DM}	$d = 0.05$ 100 × asymptotic predicted m.s.e.	$d = 0.5$ 100 × m.s.e. of $\bar{w}$	$d = 0.5$ 100 × asymptotic predicted m.s.e.	$d = 1.0$ 100 × m.s.e. of E_{DM}	$d = 1.0$ 100 × asymptotic predicted m.s.e.	$d = 1.0$ 100 × m.s.e. of $\bar{w}$	$d = 1.0$ 100 × asymptotic predicted m.s.e.
0.0	1.50	1.57	1.59	1.66	1.83	1.90	1.99	2.04
0.5	1.62	1.57	1.69	1.66	1.88	1.90	1.88	1.94
1.0	1.59	1.57	1.68	1.66	1.98	1.90	2.10	2.04
1.5	1.68	1.57	1.79	1.66	1.91	1.90	1.94	1.94
2.0	1.65	1.57	1.77	1.66	1.88	1.90	2.06	2.04
2.5	1.78	1.57	1.93	1.66	1.97	1.90	1.98	1.94
3.0	1.72	1.57	1.87	1.66	1.05	1.90	2.21	2.04
3.5	1.84	1.57	1.04	1.66	1.98	1.90	2.03	1.94
4.0	1.76	1.57	1.92	1.66	1.95	1.90	2.15	2.04

Start	$d = 1.5$ 100 × m.s.e. of E_{DM}	$d = 1.5$ 100 × Asymptotic predicted m.s.e.	$d = 1.5$ 100 × m.s.e. of $\bar{w}$	$d = 1.5$ 100 × asymptotic predicted m.s.e.	$d = 2.0$ 100 × m.s.e. of E_{DM}	$d = 2.0$ 100 × asymptotic predicted m.s.e.	$d = 2.0$ 100 × m.s.e. of $\bar{w}$	$d = 2.0$ 100 × asymptotic predicted m.s.e.
0.0	2.38	2.29	2.87	2.81	2.99	2.87	4.24	4.15
0.5	2.28	2.25	2.17	2.18	2.74	2.75	3.40	3.57
1.0	2.32	2.25	2.25	2.18	2.49	2.46	1.69	1.62
1.5	2.40	2.29	2.87	2.81	2.86	2.75	3.69	3.57
2.0	2.35	2.25	2.25	2.18	3.02	2.87	4.24	4.15
2.5	2.25	2.25	2.25	2.18	2.83	2.75	3.46	3.57
3.0	2.45	2.29	2.94	2.81	2.47	2.46	1.74	1.62
3.5	2.35	2.25	2.24	2.18	2.86	2.75	3.65	3.57
4.0	2.39	2.25	2.35	2.18	3.04	2.87	4.31	4.15

asymptotically equivalent to the mean level estimator) usually had higher m.s.e. (mean square error) than $\bar{w}$. Kershaw (1983) also contains results of simulations; these indicate that the estimator suggested by Dixon and Mood (1948) (which is also asymptotically equivalent to the mean level estimator) conforms more closely in small samples to its asymptotic predicted behaviour than the estimator of Brownlee et al. Experiments were simulated for $d = 0.5$, 1.0, 1.5 and 2.0 with starts at 0.00 (0.5) 4.00 and $\beta = \pi/\sqrt{3}$ (this is the value of β for which the logistic tolerance distribution has unit variance). In all, 2000 experiments were simulated for each set of conditions. Table 3 gives values of m.s.e.'s for Dixon and Mood's estimator (denoted by E_{DM}) and $\bar{w}$, where experiments consist of 96 observations. The m.s.e.'s are usually close to the asymptotic predicted values. The m.s.e.'s of $\bar{w}$ are always above those of E_{DM} for $d = 0.5$ and 1.0, and oscillate above and below m.s.e.'s for $\bar{w}$ for $d = 1.5$ and 2.0. Here simulations and asymptotic predictions agree well. Certainly there is no evidence to support the view that $\bar{w}$ has any advantages over E_{DM}.

5. Conclusions. There may be situations where the performance of $\bar{w}$ is better than E_{DM}, but calculations of asymptotic properties backed by simulation results have indicated that there are circumstances where E_{DM} is to be preferred. The results given in this paper allow one to explore the asymptotic mean and variance of $\bar{w}$ and E_{DM} for a wide variety of response curves. They cannot, however, be used to give confidence intervals for estimators unless one has a good estimate of the slope or scale parameter, as the variances and asymptotic predicted variances are both very dependent on such parameter values.

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REFERENCES

BROWNLEE, K. I., HODGES, J. L. and ROSENBLATT, M. (1953). The up-and-down method with small samples. *J. Amer. Statist. Assoc.* **48** 262–277.

CHOI, S. C. (1971). An investigation of Wetherill's method of estimation for the up-and-down experiment. *Biometrics* **27** 961–970.

CHUNG, K. L. (1966). *Markov Chains with Stationary Transition Probabilities*, 2nd ed. Springer, Berlin.

DIXON, W. J. and MOOD, A. M. (1948). A method for obtaining and analyzing sensitivity data. *J. Amer. Statist. Assoc.* **43** 109–126.

HARRIS, T. E. (1952). First passage and recurrence distributions. *Trans. Amer. Math. Soc.* **73** 471–486.

KERSHAW, C. D. (1983). Sequential estimation for binary response. Ph.D. thesis, University of Edinburgh.

TSUTAKAWA, R. K. (1967a). Asymptotic properties of the block up-and-down method in bio-assay. *Ann. Statist.* **38** 1822–1828.

TSUTAKAWA, R. K. (1967b). Random walk design in bio-assay. *J. Amer. Statist. Assoc.* **62** 842–856.

WETHERILL, G. B. (1966) *Sequential Methods in Statistics.* Chapman, London.
WETHERILL, G. B., CHEN, H. and VASUDEVA, R. B. (1966). Sequential estimation of quantal response curves: A new method of estimation. *Biometrika* **53** 439–454.

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