J. Hyg., Camb. (1974), **73**, 97
Printed in Great Britain

Maximum likelihood solutions for the combination of relative potencies

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(*Received* 3 *December* 1973)

SUMMARY

Two published methods for the maximum likelihood estimation of a common relative potency from a series of parallel-line assays are shown to be equivalent.

Bennett (1962) and Armitage (1970) independently published methods of obtaining a maximum likelihood estimator of a common relative potency from a series of parallel-line assays. The formulae in the two papers look quite different, and the reader is tempted to conclude that the assumptions underlying the two methods must differ in some obscure but important way. There are minor differences in assumptions, but these are quite unimportant. We show below that the two methods are algebraically equivalent and therefore give the same numerical results.

The first hurdle is to overcome the notational differences of the two papers. In the present paper we use a compromise notation which differs only a little from the other two systems.

Suppose that there are k parallel-line assays, and that in the ith of these a typical observation (the jth) on the standard preparation gives response y_{ij} at log-dose x_{ij}, and similarly the j'th observation on the test preparation gives response $y'_{ij'}$, at log-dose $x'_{ij'}$. Since the regressions of response on log-dose are assumed linear and parallel, the expected value $E(y_{ij})$ is

$$E(y_{ij}) = \alpha_i + \beta_i x_{ij}, \tag{1}$$

and, similarly,

$$E(y'_{ij'}) = \alpha'_i + \beta_i x'_{ij'}. \tag{2}$$

Let the log-potency of the test preparation in terms of the standard be μ. Then

$$\alpha'_i = \alpha_i + \beta_i \mu. \tag{3}$$

The problem is to estimate the parameters α_i, β_i and μ from the data by maximum likelihood. Bennett assumes that the distribution of the observations about their regression lines is normal, with constant variance σ^2. As is well known,

the maximum likelihood solution is then the same as that given by least squares, i.e. one seeks the values of the parameters which minimize the sum of squares of residuals of the y's from the fitted lines.

Bennett considers *two* residual sums of squares of y's: (i) Q_a, the minimum residual from k pairs of parallel lines with equations (1) and (2), but *without* the assumption (3) of constant potency ratio; (ii) Q_r, the minimum residual from pairs of parallel lines obeying the restriction (3), i.e. the required solution.

Now, if we assume a common potency μ, and if μ_0 is any estimator of μ, the best fit for the ith assay, consistent with the value μ_0, will be obtained by sliding the results for the test preparation along the log-dose axis by a distance μ_0, and fitting a single regression line for both preparations. That is, for the ith assay, given μ_0, we should fit a single line to the sets of observations

$$\{x_{ij}, y_{ij}\} \quad \text{and} \quad \{x'_{ij'}+\mu_0, y'_{ij'}\}. \tag{4}$$

The residual sum of squares of the y's, summed over the k assays, would give Q_r.

For Q_a, on the other hand, we should fit two parallel lines to the two sets of observations (4), with no restriction about the distance between them; suppose the slope is B_i. The difference $Q_r - Q_a$ is then the sum of k contributions, one for each assay, and it is well known from the analysis of covariance for two groups that the contribution for the ith assay, R_i, is

$$R_i = \frac{\{\bar{y}'_i - \bar{y}_i - B_i(\bar{x}'_i + \mu_0 - \bar{x}_i)\}^2}{\frac{1}{N'_i} + \frac{1}{N_i} + \frac{1}{S_{ixx}}(\bar{x}'_i + \mu_0 - \bar{x}_i)^2}. \tag{5}$$

The quantity inside the main brackets in the numerator of R_i is the vertical distance between the two lines fitted for Q_a; the numerator is the appropriate multiplier of σ^2 in the variance of this vertical distance.

For the desired solution, we must minimize $Q_r - Q_a = \sum_{i=1}^{k} R_i$ with respect to μ_0, giving the maximum likelihood estimator $\mu_0 = \hat{\mu}$. This quantity to be minimized is (apart from a multiplying factor) Bennett's equation (5); see also lines 4–6 above his (7). The minimization is not a straightforward algebraic problem, and Bennett does not discuss the procedure in detail.

It is convenient now to introduce some simplified notation. Write*

$$D_i = \bar{y}'_i - \bar{y}_i,$$

$$z_i = \bar{x}_i - \bar{x}'_i,$$

$$v_i = \frac{1}{N_i} + \frac{1}{N'_i},$$

and

$$u_i = \frac{1}{S_{ixx}}.$$

* This is almost the notation of Armitage (1970). His u_i and v_i are equal to the quantities defined above multiplied by σ^2, but, as he points out, a knowledge of σ^2 is not required for the solution, and this parameter is better omitted from the argument.

https://doi.org/10.1017/S0022172400023883 Published online by Cambridge University Press

Then the quantity to be minimized, ΣR_i, is, from (5),

$$\Sigma \frac{\{D_i - B_i(\mu_0 - z_i)\}^2}{v_i + u_i(\mu_0 - z_i)^2}. \tag{6}$$

Differentiating (6) with respect to μ_0, equating to zero at $\mu_0 = \hat{\mu}$, and simplifying, gives

$$\Sigma \frac{\{v_i B_i + u_i(\hat{\mu} - z_i)\, D_i\}\, \{D_i - B_i(\hat{\mu} - z_i)\}}{\{v_i + u_i(\hat{\mu} - z_i)^2\}^2} = 0. \tag{7}$$

Now, compare (7) with the two equations required by Armitage's (1970) iterative solution (his equations (1) and (2), called here (A1) and (A2)):

$$\hat{\beta}_i = \frac{\lambda_i B_i + (\hat{\mu} - z_i)\, D_i}{\lambda_i + (\hat{\mu} - z_i)^2}, \tag{A1}$$

$$\hat{\mu} = \Sigma \frac{(D_i + z_i \hat{\beta}_i)\, \hat{\beta}_i}{v_i} \Big/ \Sigma \frac{\hat{\beta}_i^2}{v_i}. \tag{A2}$$

These involve the maximum likelihood estimator $\hat{\beta}_i$ of β_i, which has not previously entered the argument. However, (A1) and (A2) are together equivalent to (7). For if $\hat{\beta}_i$ from (A1) is substituted in (A2), and the result simplified, (7) is obtained. The two solutions are equivalent. To put this another way, (A1) and (A2) provide a relatively simple iterative system for solving (7); their derivation is particularly simple (Armitage, 1970) because one may proceed from the distributions of B_i and D_i without going back to the original observations (x_{ij}, y_{ij}) and $(x'_{ij'}, y'_{ij'})$.

One advantage of Bennett's approach is that it leads to the calculation of confidence regions for μ. If μ_0 were the true value of μ, (6) would be distributed as σ^2 times a χ^2 variate on k degrees of freedom. If σ^2 is known, equating (6) to σ^2 times certain percentiles of this χ^2 distribution will give the appropriate confidence region for μ. The same solution is obtained by deriving a generalized likelihood ratio χ^2 statistic from the expression for log likelihood given by Armitage. If σ^2 is not known, a similar procedure is followed with the F distribution.

Another approach to the derivation of confidence regions for μ is to use a χ^2 variate on 1 degree of freedom, representing the improvement in fit due to using the maximum likelihood estimator $\hat{\mu}$ rather than an arbitrary value μ_0. These different approaches will be discussed further in a forthcoming joint paper with D. J. Finney.

We are grateful to Professor D. J. Finney for suggesting that the relationship between the two solutions should be explored.

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