Supplement to Oron and Flournoy, "Centered Isotonic Regression: Point and Interval Estimation for Dose-Response Studies"

Implementing and Modifying the Morris (1988) Ordered-Binomial Interval

Morris (1988) developed a specific iterative solution to the ordered-Binomial interval bound problem that conforms to the conditions of his interval-coverage proof. Assume we have m Binomial summaries at the dose levels $x_1, \ldots, x_m$, using the article's terminology, i.e., each summary represents $n_m y_m$ positive responses out of n_m observations at x_m.

For the upper bound, one defines a set of m cumulative distribution functions $G_j(x)$, $j = 1, \ldots, m$, starting with the m-th function:

$$G_m\left(y_m \mid n_m, \theta_m^{UCL}\right) = Bin_F\left(n_m y_m \mid n_m, \tilde{\theta}_m^{UCL}\right),$$

where Bin_F is the Binomial CDF and θ_m^{UCL} is the upper (forward) confidence bound at x_m. We then solve for $\tilde{\theta}_m^{UCL}$ by equating G_m to $\alpha/2$ (with $1-\alpha$ being the specified interval coverage). This produces a UCL equivalent to the Clopper-Pearson bound. For each subsequent dose level indexed $j, j = m-1, \ldots, 1$,

$$\begin{aligned} G_j\left(y_j \mid n_j, \theta_j^{UCL}\right) &= Bin_F\left(n_j y_j - 1 \mid n_j, \tilde{\theta}_j^{UCL}\right) \\ &+ \quad G_{j+1}\left(\cdot \mid \tilde{\theta}_k^{UCL}\right) Bin_f\left(n_j y_j \mid n_j, \tilde{\theta}_j^{UCL}\right), \end{aligned}$$

where Bin_f is the Binomial probability mass function for exactly $n_j y_j$ posi-

tive responses out of n_j observations. This equation defines G_j as a function of θ; the iteration works via the presence of the function G_{j+1}. The actual UCL is found as above, by equating G_j to $\alpha/2$. The equations for the LCL are analogous, using CDFs $H_j, j = 1, \ldots, m$, with the iteration proceeding from H_1 onwards.

Morris (1988)'s formulae had an apparent typo: G_{j+1} in the second equation is written as a function of $\tilde{\theta}_{j+1}^{UCL}$ rather than $\tilde{\theta}_{j}^{UCL}$ as above. Stated that way, it is already equated to $\alpha/2$, and therefore the iteration cannot proceed. With the formula as above, we were able to reproduce Morris (1988) Table 1, which calculated UCLs for the Reed and Muench (1938) dataset. The correction was verified with Morris (personal communication).

Iasonos and Ostrovnaya (2011) used a different method presented by Morris (1988): a generic formula that doesn't use the Binomial probability structure, but rather assumes normal errors. In that method, each bound incorporates a weighted average from dose j and doses to its right (for UCLs) or left (for LCLs). The user has to specify these weights.

The Morris iteration relies upon the Clopper-Pearson bounds due to their direct connection to exact Binomial probabilities, hence ensuring coverage according to Morris (1988)'s theorems. However, as mentioned in the article, there exist analytical pointwise Binomial solutions with satisfactory coverage but narrower intervals. Therefore, our code optionally replaces any UCL or LCL produced via the ordered iteration above, with an analytical pointwise bound, in case the latter is tighter. The default alternative is the Wilson bound, but the Agresti-Coull and Jeffrys are also provided in the 'cir' package. The latter Agresti-Coull interval is often known as the "plus four" interval, because it can be approximated by adding 2 to the numerator and

4 to the denominator of the raw Binomial estimate before calculating the usual asymptotic-theory standard errors.

Finally, bounds are further tightened to enforce monotonicity when applicable. For example, if $\tilde{\theta}_3^{UCL}$ has been further tightened via the Wilson interval, and is now lower than $\tilde{\theta}_2^{UCL}$, then $\tilde{\theta}_2^{UCL}$ will also receive $\tilde{\theta}_3^{UCL}$'s new value.

Bias Statistics from Forward Simulations

Conditions			Pointwise Bias at x Values				
Family	n	Method	x_2	x_3	x_4	"$x_{2.5}$"	"$x_{3.75}$"
Logistic	20	IR	0.030	-0.006	-0.016	0.004	-0.004
		CIR	-0.014	-0.002	0.018	-0.012	0.013
	40	IR	0.010	0.003	-0.006	0.009	-0.005
		CIR	-0.009	-0.001	0.006	-0.000	-0.000
	80	IR	0.001	-0.001	-0.004	0.003	-0.006
		CIR	0.001	-0.003	0.001	0.002	-0.004
Weibull	20	IR	0.026	0.002	-0.013	0.005	-0.006
		CIR	-0.034	-0.018	0.021	-0.025	0.006
	40	IR	0.006	0.004	-0.002	0.003	-0.002
		CIR	-0.033	-0.012	0.012	-0.018	0.002
	80	IR	-0.000	0.004	0.003	-0.001	-0.001
		CIR	-0.020	-0.009	0.004	-0.013	-0.003
"Staircase"	20	IR	0.011	0.000	0.004	-0.025	0.021
		CIR	-0.139	-0.031	0.124	-0.082	0.072
	40	IR	0.004	0.003	0.008	-0.023	0.019
		CIR	-0.135	-0.025	0.116	-0.073	0.063
	80	IR	0.001	-0.002	-0.001	-0.025	0.011
		CIR	-0.136	-0.032	0.106	-0.073	0.056

References

Iasonos, A., Ostrovnaya, I., 2011. Estimating the dose-toxicity curve in completed phase I studies. Stat. Med. 30, 2117–2129.

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