

TRADE-OFFS IN MODEL AVERAGING USING MULTILEVEL TESTS

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There were two errors in Wilson [1] which I have corrected [2], but I do not accept the four claimed by Goeman, Rosenblatt and Nichols [3]; I rebut them point-by-point in an appendix (<https://doi.org/10.6084/m9.figshare.9699740>). However, their letter highlights two limitations of the harmonic mean p -value (HMP) procedure that I discuss below with possible counter-measures.

First, they report a model of p -value dependence (“GRN”) with parameter $\rho = 0.2$. Unlike the dependence simulated in Figure S4 of [1], GRN dependence makes the asymptotically exact HMP anticonservative, producing a type I error rate of 0.09 when all null hypotheses are true, above the theoretical target of $\alpha = 0.05$. This limitation is important but it does not, as claimed, imply an error. The paper states that ‘the assumptions of equal weights, independence, and identical degrees of freedom can be relaxed’. A fair criticism would be that the paper did not qualify that statement sufficiently.

Equation 2.7 of Davis and Resnick[4] implies that the result that $p_{\circ} \rightarrow \overset{\circ}{p}$ as $\overset{\circ}{p} \rightarrow 0$ (Equation 5 of [1]) holds despite dependence when

$$\Pr(p_j < x \mid p_i < x) \rightarrow 0, \quad \text{as } x \rightarrow 0 \quad (1)$$

for all p -values $i \neq j$. This condition appears satisfied by GRN (Figure 1A). Simulations confirm convergence of the asymptotically exact test (Equation 4 of [1]) as α becomes small (Figure 1B). Thus Equation 1 formalises robustness of the HMP to dependence as $\alpha \rightarrow 0$, but not necessarily at $\alpha = 0.05$.

Second, Goeman, Rosenblatt and Nichols mention that the significance threshold at which the HMP rejects an individual null hypothesis should be more stringent than the Bonferroni threshold, contrary to the paper. This is a special case of the error in which the criterion for declaring set \mathcal{R} significant should be $\overset{\circ}{p}_{\mathcal{R}} \leq \alpha_L w_{\mathcal{R}}$, rather than $\overset{\circ}{p}_{\mathcal{R}} \leq \alpha_{|\mathcal{R}|} w_{\mathcal{R}}$, where L is the total number of tests and $\alpha_L \leq \alpha_{|\mathcal{R}|} < \alpha$. Thus the power of the HMP to detect significant *groups* of hypotheses comes at the cost of reduced power to detect *individual* hypotheses.

One response is to seek a test that shares some benefits of the HMP while avoiding these issues. Multilevel versions of Bonferroni and Simes’ [5] procedures are candidates, as both are robust to GRN dependence (Figure 1C). Their combined p -values for set \mathcal{R} approximate the HMP by bounding it

from above (SI Equations 36 and 39 of [1]):

$$\begin{aligned} p_{\mathcal{R}}^{\text{Bonf}} &= \frac{w_{\mathcal{R}}}{\max_{i \in \mathcal{R}} \{w_i/p_i\}} \\ p_{\mathcal{R}}^{\text{Simes}} &= \frac{w_{\mathcal{R}}}{\max_{i \in \mathcal{R}} \{r_{i\mathcal{R}} w_i/p_i\}} \\ \overset{\circ}{p}_{\mathcal{R}} &= \frac{w_{\mathcal{R}}}{\sum_{i \in \mathcal{R}} w_i/p_i} \end{aligned} \tag{2}$$

(Here $w_{\mathcal{R}} = \sum_{i \in \mathcal{R}} w_i$, $\sum_{i=1}^L w_i = 1$, and $r_{i\mathcal{R}}$ ranks w_i/p_i within \mathcal{R} from largest, 1, to smallest, $|\mathcal{R}|$.)

The multilevel Bonferroni and Simes methods can therefore be interpreted as approximating the HMP’s model averaging approach. These multilevel tests control the strong-sense familywise error rate because a superset of any significant subset must also be significant at threshold $\alpha w_{\mathcal{R}}$. This allows the most significant groups of p -values to be identified, so that conclusions are made at the finest resolution permitted by the data, as in the HMP procedure.

Multilevel HMP, Simes and Bonferroni procedures all have lower power (higher type II error rates) for combining small proportions of p -values, the HMP slightly more so. All procedures have higher power for combining large proportions of p -values, the HMP considerably more so (Figure 1D). Thus multilevel Bonferroni, Simes and HMP procedures all offer some benefits of model averaging with different trade-offs in terms of the power of their combined tests and their robustness to dependence.

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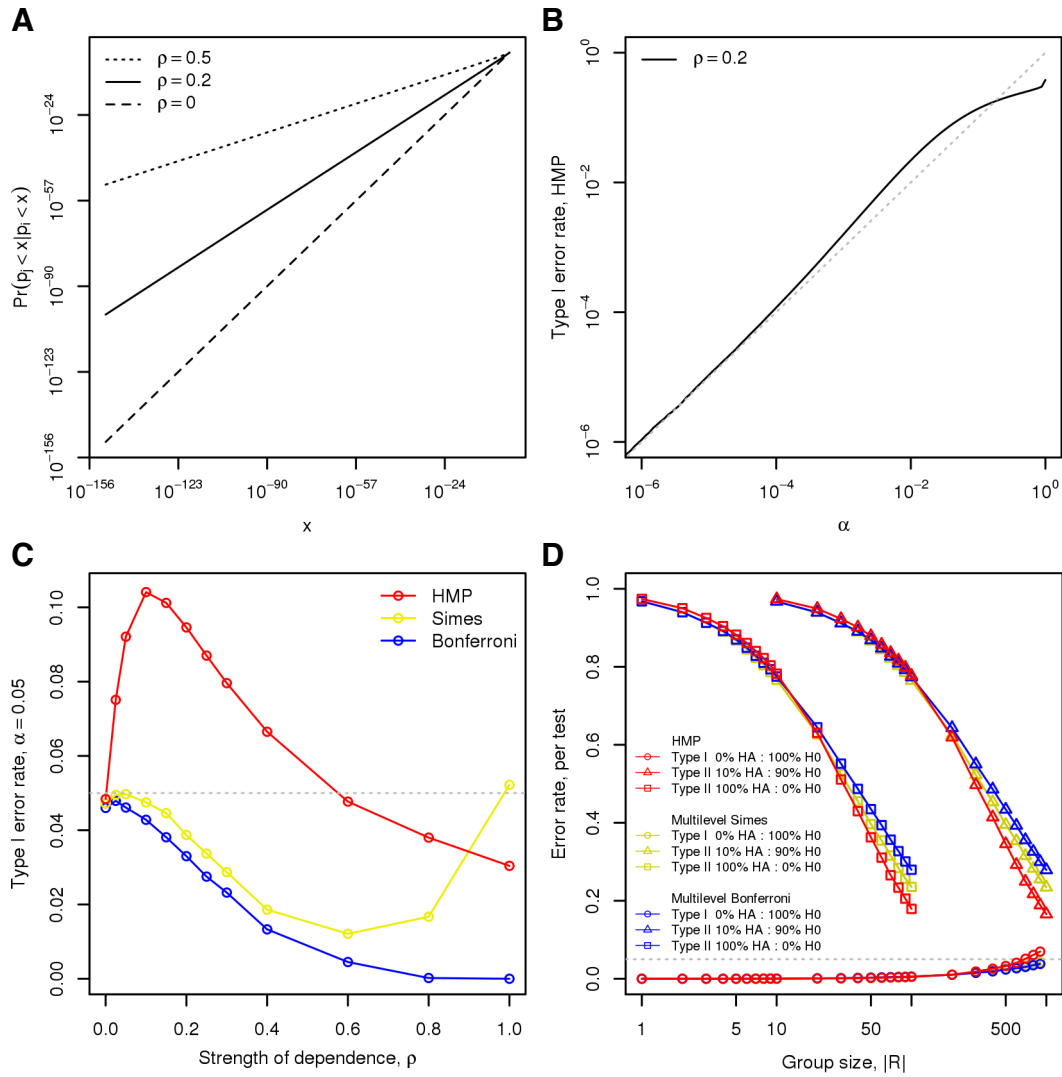


FIGURE 1. Properties of the GRN model. (A) GRN satisfies Davis and Resnick's condition. (B) For small α , the asymptotically exact HMP procedure converges to the correct type I error rate (10^8 simulations, $L = 10^5$). (C) Simes and Bonferroni are robust to GRN dependence (10^4 simulations, $L = 10^5$). (D) Error rates for multilevel Bonferroni, Simes and HMP procedures as a function of the number of p -values being combined. The $L = 1000$ normal random variables have means -2.0 and 0.0 under HA and H0 respectively in proportion 100:900 (10^4 simulations). R code: doi.org/10.6084/m9.figshare.9699743