Use of P-Values to Evaluate the Probability of a Genuine Finding in Large-Scale Genetic Association Studies

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Background & Motivation

Non-replication of association studies

- Despite a stringent multiplicity correction, most initial association findings fail to replicate in subsequent studies.
- P-value is not the probability of the null hypothesis so statistically significant P-value does not imply high chances that a finding is real.

Bayesian approach

- To decide whether a finding is false or not, a P-value can be converted to Bayesian probability that a finding is genuine.

POFIG Properties

- Unaffected by multiple testing and by selection of the most significant results (Table 1).
- POFIG average across a set of tentative associations provides False Discovery Rate estimate across these associations (Tables 2-3).
- POFIG can be used sequentially for discovery and replication studies to assess the combined probability, while accounting for correspondence in the effect direction (Fig. 2).
- As in FPRP, a single “typical” effect size can be used, but three typical effect size values (low, moderate and large) greatly reduce bias (Table 1). This bias is also greatly reduced as the number of tests increases (Table 3).

Simulations Study

- Probability that the minimum P-value is a false finding (FPRP).
- The proportion of false findings (FDR) among the 100 smallest P-values.
- The average of posterior probabilities among the 100 smallest P-values, i.e., the false discovery rate (FDR) among the 5 smallest P-values.

Previously Proposed Methods

- The approach cannot give the probability that a particular finding is false.
- Does not take into account the entire distribution of possible effects sizes, but relies on a single typical value.
- The prior distribution of effect sizes is specified in terms of the log relative risk and is assumed to be normal.
- It would be desirable to relax this distributional assumption and allow more flexibility with respect to the test statistic.

Proposed Methodology (POFIG)

\[ \Pr(H_0 | p) = \frac{f_0(p) \Pr(H_0)}{f_0(p) \Pr(H_0) + f_\gamma(p) \Pr(H_A)} = \left[ 1 + \frac{1 - \Pr(H_0)}{\Pr(H_0)} \times f_\gamma(p) \right]^{-1} \]

- POFIG: Probability that the Finding is Genuine
- \( f_\gamma(p) = \frac{\sum_{i=1}^{B} w_f(p | \gamma_i)}{\sum_{i=1}^{B} w_i} \)

In calculating this marginal density one specifies \( B \) plausible ranges of effect sizes \( \gamma \) and the number of loci with that effect size (\( m \)). The effect size is defined as a parameter of the P-value density for truly associated variants.

- Prior probability of the null:
- \( \Pr(H_0) = 1 - \sum w_i/K \)
- \( f_\gamma(p | \gamma) = \frac{g_\gamma(G_0^{-1}(1-p))}{g_0(G_0^{-1}(1-p))} \)

- Effect size: noncentrality (\( \gamma \)) in terms of the odds ratios:
- \( D = \text{the squared log of odds ratio, } N = n_1n_2/(n_1 + n_2) \)
- \( \gamma = N \times D \cdot q(1 - q) = N \times \epsilon \)

Application

Crohn’s disease P-values from Barrett et al. (2008)

- POFIG: Probability that the finding is true (POFIG).
- Probabilities are based on the estimates for the total number of susceptibility SNPs reported in Park et al. (2009) (800 susceptibility SNPs).

Limitations

- High precision in estimation of true probabilities comes at price of correct specification of the effect size distribution.
- Under the alternative, the P-value density needs to be governed by a single parameter (e.g., noncentrality or mean shift).

Table 2:

| Number of tests | \( \Pr(H_0|P_{-}\text{value}) \) | Shape |
|-----------------|----------------------------------|-------|
| \( 10^0 \)      | 0.04                             | 0.634 |
| \( 10^1 \)      | 0.06                             | 1     |
| \( 10^2 \)      | 0.08                             | 0.634 |

Figure 1:

- Distribution of posterior probabilities that a P-value is a false finding.
- First graph: Estimated probability that the smallest P-value is a false finding. Second graph: Estimated probability that the signal from the P-value is a false finding when converted to a posterior probability.

Figure 2:

- Simulations Study: Distribution of posterior probabilities that a P-value is a false finding for the total number of susceptibility SNPs reported in Park et al. (2009).