test, generating p values P_j. The evidence against the null hypothesis (1) is then measured by the rank of $P_{k'}$ in the empirical distribution, $[P_j]$, generated. This effectively compares the p value at the test SNP k conditional on SNP k' to that conditioning on all other SNPs in the region. However, note that because this method summarizes evidence for colocalisation by a rank only, there is no statistical inference attached. Thresholds for interpreting ranks would be expected to depend on SNP density and LD patterns.

The proportional approach frames the null hypothesis differently. A set of q SNPs are chosen which are deemed somehow to jointly be good predictors of one or both traits. Regressing Y and Y' against these columns of X and X' respectively produces estimates, $\mathbf{b}_1$ and $\mathbf{b}_2$, of regression coefficients $\boldsymbol{\beta}_1$ and $\boldsymbol{\beta}_2$, with variance-covariance matrices $\mathbf{V}_1$ and $\mathbf{V}_2$ respectively. Since sample sizes are large, the combined likelihood may be closely approximated by a Gaussian likelihood for $(\mathbf{b}_1, \mathbf{b}_2)$, assuming $\mathbf{V}_1, \mathbf{V}_2$ are known and that $\mathrm{Cov}(\mathbf{b}_1, \mathbf{b}_2) = 0$. Assuming equal LD in the two cohorts, i.e. that the correlation structure between the SNPs does not differ, Plagnol et al. [2009] show that the regression coefficients should be proportional and proposed testing for a shared causal variant by testing the null hypothesis

$$H_0^{\mathrm{prop}} : \boldsymbol{\beta}_1 \propto \boldsymbol{\beta}_2,$$

i.e. $\boldsymbol{\beta}_1 = \frac{1}{\eta}\boldsymbol{\beta}_2 = \boldsymbol{\beta}$. The chi-squared statistic

$$T(\eta)^2 = \mathbf{u}^T \mathbf{V}^{-1} \mathbf{u} \sim \chi^2 \tag{2}$$

is derived from Fieller's theorem [Fieller, 1954], where $\mathbf{u} = \left(\mathbf{b}_1 - \frac{1}{\eta}\mathbf{b}_2\right)$ and $\mathbf{V} = \mathbf{V}_1 + \frac{1}{\eta^2}\mathbf{V}_2$. If η were known, $T(\eta)^2$ would have a χ^2 distribution on q degrees of freedom. Plagnol et. al take a profile likelihood approach and replace η by its maximum likelihood estimate, $\hat{\eta}$, which also minimises $T(\eta)^2$. Asymptotic likelihood theory suggests that $T(\hat{\eta})^2$ has a χ^2 distribution on $q-1$ degrees of freedom. Alternatively, Wallace et al. [2012] take a Bayesian approach. They begin by reparametrising the likelihood in terms of $\theta = \tan^{-1}(\eta)$ and rewriting the null hypothesis as

$$H_0^{\mathrm{prop}} : \quad \boldsymbol{\beta}_1 = \boldsymbol{\beta}\cos(\theta); \quad \boldsymbol{\beta}_2 = \boldsymbol{\beta}\sin(\theta).$$