Text S2: Sampling variance of genetic correlation

Assume that two traits y_1 and y_2 are measured on all individuals with heritabilities of h_1^2 and h_2^2, genetic correlation of r_{G}, and phenotypic correlation of r_{P}. Assume that y_1 and y_2 are standardised so that $\mathrm{E}(y_1) = \mathrm{E}(y_2) = 0$ and $\mathrm{var}(y_1) = \mathrm{var}(y_2) = 1$. If we construct two new traits,

$z_1 = y_1 + y_2 = a_1 + e_1$ and $z_2 = y_1 - y_2 = a_2 + e_2$

where a_1 and a_2 are the genetic effects, we then have

$\mathrm{var}(z_1) = 2(1 + r_{\mathrm{P}})$, $\mathrm{var}(z_2) = 2(1 - r_{\mathrm{P}})$ and $\mathrm{cov}(z_1, z_2) = 0$

$\mathrm{var}(a_1) = h_1^2 + h_2^2 + 2h_1 h_2 r_{\mathrm{G}}$, $\mathrm{var}(a_2) = h_1^2 + h_2^2 - 2h_1 h_2 r_{\mathrm{G}}$, and $\mathrm{cov}(a_1, a_2) = h_1^2 - h_2^2$

If we denote h_{z1}^2 and h_{z2}^2 as the heritabilities for the two new traits, then

$h_{z1}^2 = \mathrm{var}(a_1) / \mathrm{var}(z_1)$ and $h_{z2}^2 = \mathrm{var}(a_2) / \mathrm{var}(z_2)$

We know from our derivations above that $\mathrm{var}(\hat{h}_{z1}^2) = \mathrm{var}(\hat{h}_{z2}^2) = 2 / [N^2 \, \mathrm{var}(A_{ij})]$, with N being the sample size and $\mathrm{var}(A_{ij})$ being the variance of the genetic relationship between individuals *i* and *j*.

We can calculate r_{G} from the equations above

$r_{\mathrm{G}} = [\mathrm{var}(a_1) - \mathrm{var}(a_2)] / [\mathrm{var}(a_1) + \mathrm{var}(a_2) - 2(h_1 - h_2)^2]$

Let $\alpha = \mathrm{var}(a_1)$, $\beta = \mathrm{var}(a_2)$ and $\Delta = 2(h_1 - h_2)^2$, then

$\hat{r}_{\mathrm{G}} = [\hat{\alpha} - \hat{\beta}] / [\hat{\alpha} + \hat{\beta} - \hat{\Delta}]$

A first order Taylor approximation of the sampling variance of $\hat{r}_{\mathrm{G}}$ is

$$\mathrm{var}(\hat{r}_{\mathrm{G}}) \approx \left(\frac{\partial \hat{r}_{\mathrm{G}}}{\partial \hat{\alpha}}\right)^2 \mathrm{var}(\hat{\alpha}) + \left(\frac{\partial \hat{r}_{\mathrm{G}}}{\partial \hat{\beta}}\right)^2 \mathrm{var}(\hat{\beta}) + 2\frac{\partial \hat{r}_{\mathrm{G}}}{\partial \hat{\alpha}} \frac{\partial \hat{r}_{\mathrm{G}}}{\partial \hat{\beta}} \mathrm{cov}(\hat{\alpha}, \hat{\beta})$$

where the sampling variance of $\hat{\Delta}$ is ignored because $\hat{\Delta}$ is likely to be small.

Since $\frac{\partial \hat{r}_{\mathrm{G}}}{\partial \hat{\alpha}} = \frac{2\hat{\beta} - \hat{\Delta}}{(\hat{\alpha} + \hat{\beta} - \hat{\Delta})^2}$ and $\frac{\partial \hat{r}_{\mathrm{G}}}{\partial \hat{\beta}} = \frac{-2\hat{\alpha} + \hat{\Delta}}{(\hat{\alpha} + \hat{\beta} - \hat{\Delta})^2}$, we can get

$$\frac{\partial \hat{r}_{\mathrm{G}}}{\partial \hat{\alpha}} = \frac{2(\hat{h}_1^2 + \hat{h}_2^2 - 2\hat{r}_{\mathrm{G}}\sqrt{\hat{h}_1^2\hat{h}_2^2}) - 2(\hat{h}_1^2 + \hat{h}_2^2 - 2\sqrt{\hat{h}_1^2\hat{h}_2^2})}{16\hat{h}_1^2\hat{h}_2^2} = \frac{1 - \hat{r}_{\mathrm{G}}}{4\sqrt{\hat{h}_1^2\hat{h}_2^2}}$$

$$\frac{\partial \hat{r}_{\mathrm{G}}}{\partial \hat{\beta}} = \frac{-2(\hat{h}_1^2 + \hat{h}_2^2 + 2\hat{r}_{\mathrm{G}}\sqrt{\hat{h}_1^2\hat{h}_2^2}) + 2(\hat{h}_1^2 + \hat{h}_2^2 - 2\sqrt{\hat{h}_1^2\hat{h}_2^2})}{16\hat{h}_1^2\hat{h}_2^2} = \frac{-1 - \hat{r}_{\mathrm{G}}}{4\sqrt{\hat{h}_1^2\hat{h}_2^2}}$$

Since $\mathrm{cov}(z_1, z_2) = 0$, $\mathrm{cov}(\hat{\alpha}, \hat{\beta}) \approx 0$ so that

$$\begin{aligned}
\mathrm{var}(\hat{r}_{\mathrm{G}}) &\approx \left(\frac{1 - \hat{r}_{\mathrm{G}}}{4\sqrt{\hat{h}_1^2\hat{h}_2^2}}\right)^2 \mathrm{var}(\hat{\alpha}) + \left(\frac{1 + \hat{r}_{\mathrm{G}}}{4\sqrt{\hat{h}_1^2\hat{h}_2^2}^2}\right)^2 \mathrm{var}(\hat{\beta}) \\
&= \frac{(1 - \hat{r}_{\mathrm{G}})^2}{16\hat{h}_1^2\hat{h}_2^2}[\mathrm{var}(z_1)]^2 \mathrm{var}(\hat{h}_{z1}^2) + \frac{(1 + \hat{r}_{\mathrm{G}})^2}{16\hat{h}_1^2\hat{h}_2^2}[\mathrm{var}(z_2)]^2 \mathrm{var}(\hat{h}_{z1}^2) \\
&= \frac{(1 - \hat{r}_{\mathrm{G}} r_{\mathrm{P}})^2 + (\hat{r}_{\mathrm{G}} - r_{\mathrm{P}})^2}{\hat{h}_1^2\hat{h}_2^2 N^2 \mathrm{var}(A_{ij})}
\end{aligned}$$

For power calculation, we can substitute the estimates with the true parameters. We then have

$$\mathrm{var}(\hat{r}_{\mathrm{G}}) \approx \frac{(1 - r_{\mathrm{G}} r_{\mathrm{P}})^2 + (r_{\mathrm{G}} - r_{\mathrm{P}})^2}{h_1^2 h_2^2 N^2 \mathrm{var}(A_{ij})}$$