SNP based pathway algorithm.

① Summary data $\{\beta_i^{(A)}, \sigma_i^{(A)}\}$ from population A

Summary data $\{\beta_i^{(B)}, \sigma_i^{(B)}\}$ from population B

② Based on the reference sample $R^{(A)}$, and reference sample $R^{(B)}$, find $maf_i^{(A)}$ and $maf_i^{(B)}$ for SNP i. find a common set of SNPs such that $Maf_i^{(A)} \geq C$ and $Maf_i^{(B)} \geq C$. (e.g. $C = 2\%$)

③ Now, we are dealing with a common set of SNPs.

④ Get the Z score for each SNP in population A and B, let them be $Z_i^{(A)}$ and $Z_i^{(B)}$, $Z_i^{(A)} := \frac{\beta_i^{(A)}}{\sigma_i^{(A)}}$

⑤ Before doing LD pruning use function from sARTP to get the covariance matrix for the Z scores of all considered SNPs in population A and B. let them be $\Sigma^{(A)}$ and $\Sigma^{(B)}$

⑥ Combine the Z scores given $\beta_i^{(A)}$, $\sigma_i^{(B)}$, $\beta_i^{(B)}$, $\sigma_i^{(B)}$, define the combined Z score for SNP i as

See update at the end.

$$Z_i = w_i^{(A)} Z_i^{(A)} + w_i^{(B)} Z_i^{(B)},$$

with

$$w_i^{(A)} = \frac{1}{\sigma_i^{(A)}} \Big/ \sqrt{\left(\frac{1}{\sigma_i^{(A)}}\right)^2 + \left(\frac{1}{\sigma_i^{(B)}}\right)^2}$$

$$w_i^{(B)} = \frac{1}{\sigma_i^{(B)}} \Big/ \sqrt{\left(\frac{1}{\sigma_i^{(A)}}\right)^2 + \left(\frac{1}{\sqrt{\sigma_i^{(B)}}}\right)^2}$$

⑦ Obtain the covariance matrix for Z_i as

$$\mathrm{Cov}(Z_i, Z_j) \triangleq \Sigma$$

$$= w_i^{(A)} \cdot w_j^{(A)} \cdot \Sigma_{ij}^{(A)} + w_i^{(B)} w_j^{(B)} \Sigma_{ij}^{(B)}$$

⑧ Given Σ, use function from sARTP to do LD pruning. obtain the final set of SNP.

⑨ Update Σ and Z_i, for the remaining SNPs, and run sARTP.

Note: We already have the covariance matrix for the Z score, you can use it to generate Z scores under the null. the other steps are the same as if we are running SARTP on data from one population.

△ Update for Step 6 for M populations

Let $Z_i^{(m)}$ be the z-score for snp i from population m

and $\beta_i^{(m)}$, $\sigma_i^{(m)}$ be the corresponding estimate and standard

error.

Obtain $Z_i = \sum_{m=1}^{M} w_i^{(m)} Z_i^{(m)}$, with

$$w_i^{(m)} = \frac{1}{\sigma_i^{(m)}} \Big/ \sqrt{\sum_{m=1}^{M} \left(\frac{1}{\sigma_i^{m}}\right)^2}$$

△ Update for Step 7.

Obtain the covariance matrix for Z_i as

$$\begin{aligned}\Sigma_{ij} &= \mathrm{Cov}(Z_i, Z_j) \\ &= \sum_{m=1}^{M} w_i^{(m)} w_j^{(m)} \mathrm{Cov}(Z_i^{(m)}, Z_j^{(m)}) \\ &= \sum_{m=1}^{M} w_i^{(m)} w_j^{(m)} \Sigma_{ij}^{(m)}\end{aligned}$$

where $\Sigma_{ij}^{(m)}$ is the covariance matrix for population m.