Credible sets in LocusZoom

Method

This method is a quick and simple approach that only requires the variant p-values. It is fast enough to recalculate on the fly as the viewable region changes.

1. Calculate a Bayes factor given $-log_{10}$ p-value for each variant:

$$\begin{aligned} p &= 10^{-log_{10} \text{ p-value}} && \text{(convert back to p-value)} \\ z &= F^{-1}(\frac{p}{2}) && \text{(inverse CDF for standard normal)} \\ BF_i &= e^{Z^2/2} && \text{(Bayes factor)} \end{aligned}$$

   The Bayes factor arises from the likelihood ratio:

$$\begin{aligned} BF &= \frac{P(x|H_1)}{P(x|H_0)} \\ &= \frac{P(x|\mu = x, \sigma)}{P(x|\mu = 0, \sigma)} \\ &= \frac{e^{-(\frac{x-x}{\sigma})^2/2}}{e^{-(\frac{x-0}{\sigma})^2/2}} \\ &= \frac{1}{e^{-(\frac{x}{\sigma})^2/2}} \\ &= e^{(\frac{x}{\sigma})^2/2} \\ &= e^{Z^2/2} \end{aligned}$$

   Unfortunately, it is possible to see very small p-values (as extreme as 10^{-500} or even smaller.) JS does not natively support $>$ 64-bit float (unless using an arbitrary precision library.)

   There is a simple approximation that works here: Z^2 is a linear function of $-log_{10}$ p-value in the domain $[\approx 10, \inf]$. For very small p-values, then, we use this approximation in place of calculating F^{-1} directly.

   It is also difficult to calculate $e^{Z^2/2}$ for large values of $Z^2/2$ (JS cannot calculate `Math.exp` for values $>$ 709.) To avoid this issue, we shift the values down by $max(Z^2/2) - 709$ (and only if any are $>$ 709.)

2. Calculate posterior probability of being causal for each variant:

$$PP_i = P(M_i|X, M) = \frac{BF_i}{\sum_{i=1}^{k} BF_i}$$

   where $i = 1..k$ indexes all the variants in the region.

3. Assign variants to the $(X * 100)\%$ credible set:

   - Sort by PP_i in descending order
   - Add the variant with the largest PP_i to the set and continue until $\sum_{i \in set} PP_i >= X$

References

Bayesian refinement of association signals for 14 loci in 3 common diseases. Nature Genetics 44, 1294-1301, 2012. Supplementary Note S1, 6.2-6.3.3. doi:10.1038/ng.2435.