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SparsePro: an efficient genome-wide fine-mapping method integrating summary statistics and functional annotations

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Abstract

Identifying causal variants from genome-wide association studies (GWASs) is challenging due to widespread linkage disequilibrium (LD). Functional annotations of the genome may help prioritize variants that are biologically relevant and thus improve fine-mapping of GWAS results. However, classical fine-mapping methods have a high computational cost, particularly when the underlying genetic architecture and LD patterns are complex. Here, we propose a novel approach, SparsePro, to efficiently conduct genome-wide fine-mapping. Our method enjoys two major innovations: First, by creating a sparse low-dimensional projection of the high-dimensional genotype data, we enable a linear search of causal variants instead of a combinatorial search of causal configurations used in most existing methods;

Second, we adopt a probabilistic framework with a highly efficient variational expectation-maximization algorithm to integrate statistical associations and functional priors. We evaluate SparsePro through extensive simulations using resources from the UK Biobank. Compared to state-of-the-art methods, SparsePro achieved more accurate and well-calibrated posterior inference with greatly reduced computation time. We demonstrate the utility of SparsePro by investigating the genetic architecture of five functional biomarkers of vital organs. We show that, compared to other methods, the causal variants identified by SparsePro are highly enriched for expression quantitative trait loci and explain a larger proportion of trait heritability. We also identify potential causal variants contributing to the genetically encoded coordination mechanisms between vital organs, and pinpoint target genes with potential pleiotropic effects. In summary, we have developed an efficient genome-wide fine-mapping method with the ability to integrate functional annotations. Our method may have wide utility in understanding the genetics of complex traits as well as in increasing the yield of functional follow-up studies of GWASs. SparsePro software is available on GitHub at <https://github.com/zhwm/SparsePro>.

1 Introduction

Establishment of large biobanks and advances in genotyping and sequencing technologies have enabled large-scale genome-wide association studies (GWASs) [1–3]. Although GWASs have revealed extensive associations between genetic variants and traits of interest, understanding the genetic architecture underlying these genetic associations remains challenging [4–6], mainly because GWASs rely on univariate regression models, which are not able to distinguish the causal variants from other variants in linkage disequilibrium (LD) [5, 7, 8].

Several statistical fine-mapping approaches have been proposed for identifying causal variants in GWASs while considering the underlying LD patterns. For instance, BIMBAM [9], CAVIAR [10] and CAVIARBF [11] estimate the posterior inclusion probabilities (PIPs) in a pre-defined locus by evaluating multivariate Gaussian likelihood enumerating all possible configurations. FINEMAP [12] accelerates the inference with a shotgun stochastic search focusing on the most

likely subset of causal configurations. However, the number of causal configurations required to evaluate can grow combinatorially as the number of causal variants increases, thus tremendously increasing the computational cost. SuSiE [13] introduces an iterative Bayesian stepwise selection algorithm for variable selection, which can also be applied to statistical fine-mapping with greatly improved computational efficiency.

Furthermore, it has been recognized that functional annotations of the genome may help prioritize variants that are biologically relevant, thus improving fine-mapping of GWAS results [8]. For example, PAINTOR [14] and RiVIERA [15] empirically estimate the impacts of functional annotations from statistical evidence, which improves the accuracy of fine-mapping but has a high computational cost, especially when multiple causal SNPs exist in the same locus. PolyFun [16] adopts stratified LD score regression [17] to partition total trait heritability into annotation-dependent heritability estimates, and uses these estimates to specify functional priors for fine-mapping methods.

In this work, we present a unified probabilistic framework called *Sparse Projections to Causal Effects* (SparsePro) for statistical fine-mapping with the capacity to incorporate functional annotations. Accompanied with an efficient variational expectation-maximization inference algorithm [18], SparsePro achieves superior accuracy in identifying causal variants as well as computational efficiency compared to the state-of-the-art approaches in both simulation studies and real data analyses. We further demonstrate the utility of SparsePro in genome-wide fine-mapping of functional biomarkers for five vital organs in human.

2 Results

2.1 SparsePro method overview

To fine-map causal SNPs, our method takes two lines of evidence (**Figure 1**). First, from estimated marginal associations between genetic variants and a complex trait of interest, accompanied by matched LD information, we can group correlated genetic variants together and assess their effects jointly. Then, we infer the contribution of each SNP towards each group of

causal effect separately to obtain posterior inclusion probabilities (PIPs). Second, optionally, if we have knowledge about any functional annotations which may be enriched for the causal SNPs, we can estimate the relative enrichment of these annotations, and re-prioritize SNPs according to the enrichments of these annotations. As outputs, our method yields PIP estimates for each SNP and enrichment estimates of candidate functional annotations.

2.2 Our contributions in the context of the existing methods

Our work is related to two existing methods, SuSiE [13] and PolyFun [16]. Inspired by the “sum of single effects” model in SuSiE, we introduce a sparse projection of the genotype in our model specification so that the identification of causal variants and estimation of causal effect sizes are separated. This sparse projection avoids exhaustively evaluating the combinatorial number of causal configurations. For inference, SuSiE adopts an iterative Bayesian stepwise selection algorithm that operates on the Bayes Factors (BFs) [13]. Here, we use a paired mean field variational inference algorithm [18] to jointly update the variational parameters for the causal effects and causal indicators of each SNP. Moreover, we have adapted our algorithm to directly work with GWAS summary statistics and provided appropriate estimates for the hyperparameters including trait variance and heritability estimates. To enable functionally informed fine-mapping, PolyFun uses genome-wide heritability estimates from LD score regression to set the functional priors for fine-mapping methods [16]. In contrast, we aggregate the genome-wide statistical fine-mapping evidence by directly maximizing the objective function of SparsePro to prioritize relevant annotations and robustly derive genome-wide functional priors.

2.3 SparsePro demonstrates superior performance in simulation

We performed simulations based on real genotype data from UK Biobank (**Online Methods**). We observed that SparsePro consistently demonstrated superior accuracy in identifying true causal variants. SparsePro without annotation (SparsePro-) achieved an area under the precision-recall curve (AUPRC) of 0.3699, higher than the AUPRC of 0.2677 by FINEMAP and the AUPRC of 0.3573 by SuSiE (**Figure 2A**). Notably, SparsePro had a substantially higher precision at

99 the same recall rates (**Figure 2A**). For example, at the recall rate of 25%, SparsePro achieved
100 greater than 95% precision, which is highly desirable in fine-mapping because only a small
101 number of the prioritized SNPs will be experimentally validated *in vivo* or *in vitro* in practice
102 (**Figure 2A**).

103 Moreover, SparsePro can incorporate functional priors (**Supplementary Table S1**) with im-
104 proved fine-mapping power. SparsePro+ achieved an AUPRC of 0.4636, outperforming both
105 functionally informed FINEMAP (AUPRC = 0.3088) and functionally informed SuSiE (AUPRC
106 = 0.4042) with functional priors derived by PolyFun. As expected, we also found that the per-
107 formance of SparsePro was not sensitive to the pre-specified number of independent causal
108 effects (**Supplementary Table S2** and **Supplementary Notes**).

109 Compared to FINEMAP and SuSiE, the PIPs yielded by SparsePro appeared to be much
110 more calibrated. It has been shown that for a well-calibrated fine-mapping method, the mean
111 PIP of all SNPs with a PIP above a certain threshold should be equal to the precision if these
112 SNPs were to be considered causal variants [16]. Here, we found that the mean PIP of all SNPs
113 considered to be causal variants by SparsePro was almost identical to the desired precision at
114 any threshold (**Figure 2B**). In contrast, the PIPs generated by FINEMAP and SuSiE appeared
115 to be inflated (**Figure 2B**).

116 For instance, if SNPs with a $PIP > 0.8$ were to be considered as causal variants, SparsePro-
117 and SparsePro+ would both have a median precision across simulations of 95% and 100%
118 respectively (**Figure 2C**). The selected SNPs by FINEMAP (median precision = 50% only)
119 and SuSiE (median precision = 71% only) included an excessive proportion of false positives,
120 even with functional priors (median precision = 77% for FINEMAP and 79% for SuSiE; **Fig-
121 ure 2C**). The high precision by SparsePro was consistent for all frequently used PIP thresholds
122 (**Figure 2C**) although FINEMAP and SuSiE sometimes have a slightly higher recall.

123 Furthermore, SparsePro conferred not only higher fine-mapping precision, but also higher
124 computational efficiency. In our simulation, it took only an hour to fine-map chromosome 22,
125 which was 6.5 times faster than FINEMAP and 3 times faster than SuSiE (**Figure 2D** and **Sup-
126 plementary Table S3**).

2.4 Fine-mapped SNPs by SparsePro are more enriched in tissue-specific eQTL and confer higher trait heritability

We performed GWAS in the UK Biobank [1] for five functional biomarkers: FEV1-FVC ratio (lung function), estimated glomerular filtration rate (kidney function), pulse rate (heart function), total protein (liver function) and blood glucose level (pancreatic islet function). Genome-wide fine-mapping of five functional biomarkers based on the UK Biobank population using SparsePro identified multiple potentially causal variants (**Supplementary Table S4**). To assess biological relevance of the fine-mapping results, we estimated the relative enrichment of causal signals in tissue-specific eQTL for each trait (**Materials and Methods**). We found that the fine-mapped SNPs were significantly enriched in tissue-specific eQTL for all five biomarkers, while results based on SparsePro-/+ showed the strongest enrichment (**Figure 3A**). For example, for total protein, the fine-mapped SNPs determined by SparsePro- were 4.00-fold (95% CI: 3.25-4.92) more likely to be liver-specific eQTL than non-fine-mapped SNPs, compared to a 1.54-fold (95% CI: 1.35-1.75) enrichment based on fine-mapped SNPs by SuSiE. While SuSiE was substantially improved by functional priors derived from PolyFun with a 2.20-fold (95% CI: 1.97-2.45) enrichment, the fine-mapped SNPs by SparsePro+ exhibited the highest biological relevance, being 4.06-fold (95% CI: 3.31-4.97) more likely to be liver-specific eQTL.

Moreover, at most PIP thresholds, the SNPs fine-mapped by SparsePro- explained a higher proportion of phenotypic variance based on all UK Biobank subjects (**Methods**) compared to the same number of the most likely causal SNPs identified by SuSiE (**Figure 3B** and **Supplementary Table S5**). With the functional annotations (**Supplementary Table S5**), the fine-mapped SNPs by SparsePro+ consistently achieved a higher SNP heritability for estimated glomerular filtration rate, FEV1-FVC ratio, as well as total protein compared to the PolyFun-informed SuSiE; although for glucose and pulse rate, PolyFun-informed SuSiE was able to identify SNPs with a slightly higher predictive performance at certain PIP thresholds (**Figure 3C** and **Supplementary Table S6**).

2.5 Pleiotropic effects of SNPs rs1260326 and rs5742915 on the functions of multiple vital organs

Overall, we observed considerable polygenicity for the five biomarkers of the vital organs (**Figure 4A**). Interestingly, at the PIP threshold of 0.80, we found two potentially causal variants for three of the five biomarkers. Specifically, SNP rs1260326 (**Figure 4B**), a missense variant (Leu446Pro) in gene *GCKR*, was fine-mapped for glomerular filtration rate (PIP = 1.000), blood glucose level (PIP = 0.998), pulse rate (PIP = 0.823) and total protein level (PIP = 1.000). Notably, this specific variant has been found to be significantly associated with a wide variety of glycemic traits [19] and other quantitative traits for metabolic syndromes and comorbidities [20, 21], and has been implicated in the functions of liver and other vital organs [22–24].

Another SNP, rs5742915 (**Figure 4C**), a missense variant (Phe645Leu) in gene *PML* was fine-mapped for FEV1-FVC ratio (PIP = 0.858), pulse rate (PIP = 1.000) and total protein level (PIP = 0.987). This variant has also been associated with other quantitative biomarkers of polygenic traits featuring development and metabolism, including birth weight [25], height [26], appendicular lean mass [27], and age at menarche [28]. These findings, along with other SNPs exhibiting pleiotropic effects at somewhat lower PIP thresholds (**Supplementary Table S4**) presented promising genetic targets for experimental validations in a larger effort towards understanding the mechanisms of genetic coordination among vital organs.

3 Discussion

Accurately identifying trait-determining and disease-causing variants is fundamental in genetics and particularly important for appropriately interpreting GWAS results [5, 8]. In this work, we developed SparsePro, an efficient fine-mapping method to help prioritize causal variants for complex traits, possibly with prior functional information. Through genome-wide simulations, we showed that SparsePro was highly accurate and computationally efficient compared to existing methods. By fine-mapping genetic associations with five biomarkers for vital organ functions, we demonstrated that SparsePro identified candidate variants that were biologically relevant,

179 including two variants with pleiotropic effects, which might indicate genetically encoded coordi-
180 nation among vital organs.

181 Compared to the existing methods, SparsePro has three important features. First of all, we
182 use an efficient variational inference algorithm to approximate the posterior distribution of the
183 causal variant indicators instead of exhaustively searching through all possible causal config-
184 urations or performing stepwise regression. As a result, SparsePro can be significantly faster
185 than the existing fine-mapping methods, such as FINEMAP [12], and is more than twice as
186 fast as SuSiE [13], which is a similar variable selection framework but implements an itera-
187 tive Bayesian stepwise selection procedure. The substantially improved computational effi-
188 ciency enables statistical fine-mapping of large chunks of the genome instead of analyzing
189 genetic associations on a per-locus basis as in most existing follow-up studies of GWASs. In
190 our simulation studies, compared to locus-wise fine-mapping based on COJO-identified lead
191 SNPs, such a genome-wide fine-mapping requires neither a pre-specified p-value threshold
192 (e.g. $p < 5 \times 10^{-8}$) for determining candidate loci nor an arbitrary number of causal effects per
193 locus. If functional annotations are available, the estimation of functional enrichment may also
194 be more robust by including more variants with little additional computational overhead.

195 Second, we utilize a paired mean field variational family, where the causal effect and the ca-
196 sual indicator are coupled in the variational distribution. This ensures that our approximation
197 matches closely with the true posterior distribution of the causal variant indicators [18]. As a
198 result, SparsePro yielded better-calibrated PIPs compared to existing fine-mapping methods.

199 Third, given GWAS summary statistics, we provide estimates for hyperparameters including
200 τ_y and τ_β that are reasonable in the context of polygenic trait genetics. Consequently, at several
201 commonly used PIP thresholds for defining causal variants, SparsePro showed improved con-
202 trol of false positives, demonstrated higher precision in identifying causal variants in simulation
203 and obtained stronger enrichment for tissue-specific eQTL in real data application.

204 Last, we propose and implement a probabilistic model that coherently integrates statistical
205 evidence and functional prior information. The key difference between SparsePro+ and other
206 methods that leverage functional priors, such as PolyFun [16] and PAINTOR [14], is that each
207 annotation is tested for its relevance with the trait of interest before being used to derive the

priors in our model. Therefore, functional annotations serve as complementary evidence when statistical evidence is not sufficient to discern causal variants. Based on our results, it seems that this approach distills better prior information from the functional annotations compared to the aforementioned methods.

We note that SparsePro can be further improved with the following future directions. First, SparsePro generally requires that the supplied LD reference panel matches well with that of the GWAS study population to guarantee proper convergence. While we advocate the public availability of the in-sample LD information along with the GWAS summary statistics, a more robust model is needed to account for mismatched LD information. Second, SparsePro currently supports only binary annotations while compatibility with continuous annotations is also desirable. Last, the current variational expectation-maximization scheme might not accurately estimate the joint enrichment of highly correlated annotations. Performing variable selection beforehand or effectively aggregating enrichment estimates may enable the inclusion of multiple correlated informative annotations, such as cell type-specific annotations to further improve the utility of SparsePro.

In summary, SparsePro is an efficient genome-wide fine-mapping method with the ability of integrate functional annotations. We envision its wide utility in understanding the genetic architecture of complex traits, identifying target genes, and increasing the yield of functional follow-up studies of GWASs.

4 Online Methods

4.1 SparsePro model specification

We assume the following data generative process (**Figure 1**) for a continuous polygenic trait. First, the prior probability $\tilde{\pi}_g$ for the g -th SNP ($g \in \{1, \dots, G\}$) being causal is defined as:

$$\tilde{\pi}_g = \text{softmax}(\mathbf{A}_g \mathbf{w}) = \frac{\exp(\mathbf{A}_g \mathbf{w})}{\sum_{g'=1}^G \exp(\mathbf{A}_{g'} \mathbf{w})}$$

229 where $\mathbf{A}_g$ is the $1 \times M$ annotation row vector of M candidate annotations for the g -th SNP; and
 230 $\mathbf{w}$ is the $M \times 1$ vector of logarithm of relative enrichment. Here, we use the *softmax* function
 231 to ensure the prior probabilities sum up to 1. If no functional information is provided, the prior
 232 probability of being causal is considered equal for all SNPs, i.e. $\tilde{\pi}_g = \frac{1}{G}$.

We assume that there exist K independent causal effects, and that

$$\mathbf{s}_k \sim \text{Multinomial}(1, \tilde{\boldsymbol{\pi}})$$

233 where $\tilde{\boldsymbol{\pi}} = (\tilde{\pi}_1, \dots, \tilde{\pi}_G)$ and $\mathbf{s}_k$ is a binary indicator vector of length G indicating which SNP is the
 234 causal SNP under the k -th ($k \in \{1, \dots, K\}$) causal effect.

Then, the causal effect sizes are sampled from a normal distribution, i.e.

$$\beta_k \sim \mathcal{N}(0, \tau_{\beta_k}^{-1})$$

Finally, the continuous trait $\mathbf{y}_{N \times 1}$ over N individuals is generated as follows:

$$\mathbf{y} = \mathbf{X} \sum_k \mathbf{s}_k \beta_k + \boldsymbol{\epsilon}$$

or in matrix form:

$$\mathbf{y} = \mathbf{X} \mathbf{S} \boldsymbol{\beta} + \boldsymbol{\epsilon}$$

235 where $\mathbf{X}_{N \times G}$ is the full genotype matrix, $\mathbf{S}_{G \times K}$ is the sparse projection matrix, $\boldsymbol{\beta}_{K \times 1}$ is the causal
 236 effect vector, and $\boldsymbol{\epsilon}_{N \times 1} \sim \mathcal{N}(0, \tau_y^{-1} \mathbf{I}_N)$ denotes the variance not attributable to the modelled ge-
 237 netic effects.

238 4.2 A variational inference algorithm for Bayesian fine-mapping

With this model specification (**Figure 1**), finding the causal variants is equivalent to inferring the sparse projections $\mathbf{s}_k$ and the effect sizes β_k given $\mathbf{y}$ and $\mathbf{X}$ for $k \in \{1, \dots, K\}$:

$$p(\mathbf{S}, \boldsymbol{\beta} | \mathbf{y}, \mathbf{X}, \tilde{\boldsymbol{\pi}}, \tau_{\beta}, \tau_y) = \frac{p(\mathbf{y}, \mathbf{S}, \boldsymbol{\beta} | \mathbf{X}, \tilde{\boldsymbol{\pi}}, \tau_{\beta}, \tau_y)}{p(\mathbf{y} | \mathbf{X}, \tilde{\boldsymbol{\pi}}, \tau_{\beta}, \tau_y)}$$

As the number of possible causal configurations grows combinatorial with G , the exact posterior solution is intractable because of the marginal likelihood in the denominator. Unlike most existing fine-mapping approaches using sampling-based methods to search through a subset of possible causal configurations [12, 29], we adopt a paired mean field factorization of variational family to approximate the posterior [18]:

$$q(\mathbf{S}, \boldsymbol{\beta}) = \prod_k q(\mathbf{s}_k, \beta_k) = \prod_k q(\mathbf{s}_k) q(\beta_k | \mathbf{s}_k)$$

239 This variational distribution preserves the dependency between $\mathbf{s}_k$ and β_k . It has been shown
 240 that the paired mean field variational family has similar mode and shape as the desired poste-
 241 rior distribution, and that such inference can achieve high accuracy with substantially improved
 242 computational efficiency [18].

To find the best approximation, we minimize the Kullback-Leibler (KL) divergence between the posterior distribution and the proposed variational distribution, which is equivalent to maximizing the evidence lower bound (ELBO) [30]:

$$ELBO = E_q[\log p(\mathbf{y}, \mathbf{S}, \boldsymbol{\beta} | \mathbf{X}, \tilde{\boldsymbol{\pi}}, \tau_{\beta}, \tau_y)] - E_q[\log q(\mathbf{S}, \boldsymbol{\beta})]$$

243 Based on the mean field assumptions [18], this optimization can be conducted iteratively for
 244 the k^{th} causal effect and the g^{th} SNP with the following closed-form updates until convergence
 245 (derivation details are available in **Supplementary Notes**).

We update posterior effect size for the g -th SNPs in the k -th causal effect:

$$\mu_{kg}^* = \frac{\tau_y}{\tau_{kg}^*} (\mathbf{X}_g^\top \mathbf{y} - \mathbf{X}_g^\top \mathbf{X} \sum_{k' \neq k} \gamma_{k'}^* \circ \mu_{k'}^*) \quad (1)$$

with

$$\tau_{kg}^* = \mathbf{X}_g^\top \mathbf{X}_g \tau_y + \tau_{\beta_k} \quad (2)$$

where $\circ$ represents element-wise multiplication of vectors.

We then update the posterior probability of the g -th SNP being causal in the k -th causal effect:

$$\gamma_{kg}^* = \text{softmax}(\log \tilde{\pi}_g - \frac{1}{2} \log \frac{\tau_{kg}^*}{2\pi} + \frac{\tau_{kg}^* \mu_{kg}^{*2}}{2}) \quad (3)$$

For fine-mapping, we take the maximum of these K probabilities as the PIP for SNP g : $\gamma_g^* = \max(\gamma_{1g}^*, \dots, \gamma_{Kg}^*)$.

4.3 Adaptation to GWAS summary statistics

The above variational inference algorithm requires access to large datasets containing both individual-level genotype $\mathbf{X}$ and phenotype data $\mathbf{y}$. Since a growing number of GWASs have released publicly available summary statistics (i.e., marginal effect size estimate $\hat{\beta}_g$ and its standard error se_g for the g -th SNP), we adapt SparsePro to directly operate on these summary statistics with additional information from an LD reference panel (i.e. estimates of pairwise SNP-SNP Pearson correlation).

Specifically, if we have reasonable surrogates for $\mathbf{X}_g^\top \mathbf{X}_g$, $\mathbf{X}^\top \mathbf{X}$ and $\mathbf{X}_g^\top \mathbf{y}$, we can plug them into Equations (1), (2), and (3). We include two forms of reformulation depending on whether the genotypes are standardized to have zero mean and unit variance in the GWAS.

1. If the genotypes are standardized, we have

$$\mathbf{X}_g^\top \mathbf{X}_g = N$$

$$\mathbf{X}^\top \mathbf{X} = N * LD$$

$$\mathbf{X}_g^\top \mathbf{y} = N \hat{\beta}_g$$

where N is the sample size.

2. If the genotypes are not standardized, we have

$$\hat{\beta}_g = (\mathbf{X}_g^\top \mathbf{X}_g)^{-1} \mathbf{X}_g^\top \mathbf{y}$$

$$se_g = \sqrt{var(\mathbf{y})(\mathbf{X}_g^\top \mathbf{X}_g)^{-1}}$$

Therefore,

$$\mathbf{X}_g^\top \mathbf{X}_g = \frac{var(\mathbf{y})}{(se_g^2)}$$

$$\mathbf{X}^\top \mathbf{X} = LD * (\mathbf{se}^\top \mathbf{se})$$

$$\mathbf{X}_g^\top \mathbf{y} = \mathbf{X}_g^\top \mathbf{X}_g * \hat{\beta}_g$$

Notably, if $\mathbf{y}$ has been standardized to have unit variance prior to a GWAS, we naturally supply $var(\mathbf{y}) = 1$. Otherwise, it can be estimated as $var(\mathbf{y}) = 2Np(1 - p)se^2$ where N (the study sample size), p (minor allele frequencies), and se (standard errors of effect size estimates) are usually available in GWAS summary statistics.

4.4 Variational expectation-maximization for integrating functional annotations

To estimate the relative enrichment of functional annotations and further prioritize variants, we adopt a variational expectation-maximization scheme to maximize ELBO with respect to the logarithm of relative enrichment ($\mathbf{w}$) first and then use the estimate $\hat{\mathbf{w}}$ to calculate $\tilde{\pi}_g$ (prior probability of being causal) for each SNP.

Suppose we have M candidate annotations and A_{gm} ($m \in \{1, \dots, M\}$) is a 0/1 indicator denoting whether the g -th SNP has the m -th annotation. By setting the derivative of ELBO with respect to w_m to 0 and solving for w_m , we have the following estimate for the logarithm of rele-

vant enrichment (detailed in **Supplementary Notes**),

$$w_m = \log\left(\frac{r_1/r_0}{k_1/k_0}\right)$$

where

$$\begin{aligned} k_1 &= \sum_g [A_{gm} = 1] \text{softmax}\left(\sum_{m' \neq m} A_{gm'} w_{m'}\right) \\ k_0 &= \sum_g [A_{gm} = 0] \text{softmax}\left(\sum_{m' \neq m} A_{gm'} w_{m'}\right) \\ r_1 &= \sum_{k,g} [A_{gm} = 1] \gamma_{kg}^* \\ r_0 &= \sum_{k,g} [A_{gm} = 0] \gamma_{kg}^* \end{aligned}$$

We note that this metric is equivalent to the logarithm of a relative risk, thus its standard error can be calculated as

$$se(w_m) = \sqrt{\frac{1}{r_1} + \frac{1}{r_0} - \frac{1}{k_1} - \frac{1}{k_0}}$$

We evaluate the significance of annotation enrichment with the log likelihood ratio test (G-test) [31]. Only annotations which demonstrate statistical significance are included in our model to update the prior probability of being causal for each SNP. Specifically,

$$\tilde{\pi}_g = \text{softmax}\left(\sum_m A_{gm} \hat{w}_m\right)$$

274 This functionally informed prior helps prioritize causal SNPs in addition to statistical evidence.

275 4.5 Hyperparameter settings

276 We have three hyperparameters: number of causal effect K , inverse of the unexplained vari-
277 ance τ_y and inverse variance of causal effect sizes τ_{β_k} in our model. As we show in **Supple-**
278 **mentary Notes**, our model is not sensitive to the setting of K as long as K is larger than the

279 actual number of independent effects, except that increasing K marginally increases the com-
280 putation time.

281 We set τ_y as

$$\tau_y = \frac{1}{\text{var}(y) * (1 - h^2)}$$

282 where h^2 is the local SNP heritability that can be estimated by a modified Heritability Estimation
283 from Summary Statistics (HESS) [32] based on GWAS summary statistics (**Supplementary**
284 **Notes**)

285 We set τ_{β_k} as

$$\tau_{\beta_k} = \frac{k}{\text{var}(y) * h^2}$$

286 for each of the independent causal effects. We use $k \in \{1, \dots, K\}$ to account for different effect
287 sizes and to improve model identifiability.

288 4.6 Simulation studies

289 We conducted simulations to showcase the efficiency and utility of our method. We leveraged
290 resources from the UK Biobank [1]. Specifically, we first retained 353,606 White British an-
291 cestry participants by excluding one individual from each pair of closely related individuals
292 (who had a 3rd degree or closer relationship). We then retrieved the genotypes of these indi-
293 viduals based on 271,699 SNPs which had a minor allele frequency ≥ 0.001 and an imputa-
294 tion quality score ≥ 0.6 on chromosome 22. Next, we sampled 50 causal SNPs with a two-
295 fold relative enrichment amongst SNPs that were annotated as “conserved sequences” [33],
296 “DNase I hypersensitive sites” (DHS) [34], “non-synonymous” [35], or that overlapped with his-
297 tone marks H3K27ac [36] or H3K4me3 [34]. We used the GCTA GWAS simulation pipeline [37]
298 to simulate a continuous trait with a per-chromosome heritability of 0.01. We tested the associ-
299 ation between each SNP and this simulated trait, and obtained GWAS summary statistics using
300 the fastGWA software [38]. This process was replicated 22 times to imitate a GWAS. We ob-

301 tained LD information calculated using the UK Biobank participants from https://alkesgroup.broadinstitute.org/UKBB_LD/ [16]. These LD matrices were generated for genome-wide
302 SNPs binned into sliding windows of 3 Mb where two neighboring windows had a 2-Mb over-
303 lap.
304

305 We applied SparsePro to the GWAS summary statistics with the above LD information, and
306 iterated over all sliding windows, first without any functional annotation information. We de-
307 noted the fine-mapping results as “SparsePro-”. Next, we aggregated the results from all 22
308 replications to estimate the relative enrichment for ten binary functional annotations. In addition
309 to the five annotations simulated to be enriched of causal SNPs, we also included five anno-
310 tations without enrichment: “actively transcribed regions” [39], “transcription start sites” [39],
311 “promoter regions” [40], “5’-untranslated regions” [35], and “3’-untranslated regions” [35].

312 Annotations with a G-test p-value $< 1 \times 10^{-6}$ were selected to conduct functionally informed
313 fine-mapping, and the results were denoted as “SparsePro+”. τ_β and τ_y were set according to
314 aforementioned empirical estimates. PIPs for SNPs in the 1-Mb centre of each 3-Mb sliding
315 window were extracted.

316 4.7 Method comparisons using simulated data

317 We also performed fine-mapping with some of the state-of-the-art methods. To perform fine-
318 mapping with conditional and joint (COJO) analyses [41] and FINEMAP [12], we first selected
319 COJO lead SNPs based on GWAS summary statistics by performing stepwise model selec-
320 tion implemented in the GCTA-COJO software [37]. We then applied FINEMAP with shotgun
321 stochastic search to SNPs in a 1-MB window centered at each COJO-identified lead SNP. We
322 wrote an in-house script using the “susie_rss” function to perform genome-wide fine-mapping
323 with SuSiE in the same sliding windows as SparsePro. We aggregated summary statistics from
324 22 replications and used PolyFun with the “baselineLF2.2.UKB” model [16] to calculate func-
325 tional priors. The “baselineLF2.2.UKB” model contained all annotations used in SparsePro as
326 well as additional pre-computed LD-related annotations for optimal performance of PolyFun
327 [16]. The estimated priors were provided to SuSiE via “prior_weights” and to FINEMAP via the

328 --prior-snp option, respectively. The maximal number of causal SNPs in each locus was set
329 to 5 for all methods.

330 We compared the performance of these methods in terms of precision (1 - false discovery
331 rate), recall, calibration of PIPs, as well as computation time, all evaluated on a 2.1 GHz CPU
332 node on Compute Canada.

333 4.8 Fine-mapping genetic determinants of functional biomarkers for vital 334 organs

335 To investigate the genetic coordination mechanisms of vital organs, we performed GWAS in
336 the UK Biobank [1] for five functional biomarkers: forced expiratory volume in one second to
337 forced vital capacity (FEV1-FVC) ratio for lung function, estimated glomerular filtration rate for
338 kidney function, pulse rate for heart function, total protein for liver function and blood glucose
339 level for pancreatic islet function. For each trait, we first regressed out the effects of age, age²,
340 sex, genotyping array, recruitment centre, and the first 20 genetic principal components before
341 inverse normal transforming the residuals to z-scores that had zero mean and unit variance.
342 We then performed GWAS analysis on the resulting z-scores with the fastGWA software [37,
343 38] to obtain summary statistics.

344 Using the summary statistics and the matched LD information [16], we performed genome-
345 wide fine-mapping with SparsePro-, SparsePro+, SuSiE and PolyFun-informed SuSiE as de-
346 scribed in the simulation analyses (**Section 4.7**), except that the number of causal effects was
347 set to 9 for each LD region to account for potentially more causal variants.

348 To evaluate the biological relevance of SNPs fine-mapped by different methods, we assessed
349 their relative enrichment in tissue-specific expression quantitative loci (eQTL). Tissue-specific
350 eQTL identified in the most recent release of the Genotype-Tissue Expression (GTEx) project
351 [42, 43] were obtained from <https://gtexportal.org/home/datasets>. The eQTL information
352 was not used by any functionally informed fine-mapping methods.

353 Additionally, we calculated trait heritability conferred by fine-mapped SNPs with SparsePro-
354 and SparsePro+, respectively, at several commonly used PIP thresholds for determining causal

355 variants: 0.50, 0.80, 0.90, 0.95, and 0.99. The adjusted R^2 obtained from multivariate linear re-
356 gression of the z-scores (i.e. inverse normal transformed trait residuals after regressing out co-
357 variate effects) against all fine-mapped SNPs was used as a surrogate of the SNP heritability.
358 We compared these results to heritability captured by the same number of SNPs fine-mapped
359 by SuSiE and PolyFun-informed SuSiE, separately at each PIP threshold. For instance, if SparsePro-
360 identified J SNPs with a $PIP > 0.5$, we would select J SNPs with the highest PIP determined
361 by SuSiE and compare the adjusted R^2 . Notably, this analysis evaluates predictive associations
362 instead of actual causality, hence the adjusted R^2 is not a direct indicator of the validity of the
363 fine-mapping results.

364 We selected SNPs with a $PIP > 0.8$ to explore possible pleiotropic effects using phenogram
365 [44]. Loci with potential pleiotropic effects were visualized using LocusZoom [45].

5 Figure Legends

Figure 1. SparsePro overview. The data generating process of SparsePro is depicted in a plate model with shaded nodes represent observed variables and unshaded nodes represent latent variables. The trait y is generated from K causal effects, where the k -th causal effect size $\beta_k \sim \mathcal{N}(0, \tau_{\beta_k})$. We use a sparse projection $\mathbf{s}_k \sim \text{Multinomial}(1, \hat{\boldsymbol{\pi}})$ of genotype to indicate causal variant for the k -th effect. Given the causal effect sizes and sparse indicators of causal variants, the target trait y_i for individual i follows a normal distribution $y_i \sim \mathcal{N}(\mathbf{X}_i \sum_k \mathbf{s}_k \beta_k, \tau_y^{-1})$. To help prioritize variants with functional annotations, we assume the prior probability of being causal $\hat{\pi}_g$ for the g -th variant as $\hat{\pi}_g = \text{softmax}(\mathbf{A}_g \mathbf{w})$ where $\mathbf{A}_g$ is a $M \times 1$ functional annotation vector and $\mathbf{w}$ is the $M \times 1$ vector of annotation enrichment coefficients. We adopt an efficient variational inference algorithm to jointly estimate both causal effect sizes and sparse indicators and an expectation-maximization scheme for estimating annotation enrichment coefficients $\mathbf{w}$ as detailed in Section 4.

Figure 2. SparsePro demonstrated improved accuracy and computational efficiency in genome-wide simulation results. (A) Precision-Recall curves. The inset shows the area under the precision recall curve (AUPRC) for each method. (B) Calibration of posterior inclusion probabilities (PIPs). The y-axis is the mean PIPs for all SNPs considered as causal variants, corresponding to the expected precision at different PIP cutoffs. The x-axis represents the actual precision at different PIP cutoffs. The black dashed line indicates an optimal calibration, where the expected precision perfectly matches the observed precision. (C) Precision and recall rates obtained at five frequently used PIP thresholds. Error bars indicate inter-quartile ranges. (D) Comparison of computational time. Boxes denote inter-quartile ranges and the line inside each box indicates the median running time. The color legends are displayed at the bottom of the figure.

Figure 3. Biological relevance of fine-mapped SNPs for five biomarkers, each for a distinct vital organ. (A) Relative enrichment of causal signals in tissue-specific eQTL. Target traits and

the corresponding organs are indicated. Estimates of relative enrichment with 95% confidence intervals are plotted on a logarithmic scale. (B) Comparison of the proportion of total trait variance explained by fine-mapped SNPs between SparsePro- and SuSiE. (C) Comparison of the proportion of total variance explained by fine-mapped SNPs between SparsePro+ and PolyFun informed SuSiE. Fine-mapped SNPs were identified at five PIP thresholds. As a surrogate of SNP heritability, the proportion of trait variance explained was obtained from multivariate linear regression adjusted R^2 . In this multivariate regression, we regress the inverse normal transformed trait residuals against all fine-mapped SNPs after adjusting for covariate effects. We selected the same number of top-ranked SNPs for each method separately at each PIP threshold (Materials and Methods).

Figure 4. Fine-mapping genetic associations for five functional biomarkers of vital organs. (A) Illustration of genome-wide distribution of fine-mapped SNPs on 22 chromosomes. SNPs with a posterior inclusion probability > 0.80 were indicated as colored solid circles. Two loci with potential pleiotropic effects on four and three vital organ biomarkers respectively were highlighted by red dashed rectangles. Locus zoom plots were presented for these two loci: (B) locus with fine-mapped SNP rs1260326. and (C) locus with fine-mapped SNP rs5742915. SNPs in a ± 500 kb window are included, colored by r^2 with the corresponding fine-mapped SNP.

Figure 1: SparsePro overview. The data generating process of SparsePro is depicted in a plate model with shaded nodes represent observed variables and unshaded nodes represent latent variables. The trait y is generated from K causal effects, where the k -th causal effect size $\beta_k \sim \mathcal{N}(0, \tau_{\beta_k})$. We use a sparse projection $s_k \sim \text{Multinomial}(1, \hat{\pi})$ of genotype to indicate causal variant for the k -th effect. Given the causal effect sizes and sparse indicators of causal variants, the target trait y_i for individual i follows a normal distribution $y_i \sim \mathcal{N}(\mathbf{X}_i \sum_k s_k \beta_k, \tau_y^{-1})$. To help prioritize variants with functional annotations, we assume the prior probability of being causal $\hat{\pi}_g$ for the g -th variant as $\hat{\pi}_g = \text{softmax}(\mathbf{A}_g \mathbf{w})$ where $\mathbf{A}_g$ is a $M \times 1$ functional annotation vector and $\mathbf{w}$ is the $M \times 1$ vector of annotation enrichment coefficients. We adopt an efficient variational inference algorithm to jointly estimate both causal effect sizes and sparse indicators and an expectation-maximization scheme for estimating annotation enrichment coefficients $\mathbf{w}$ as detailed in Section 4.

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420 **7 Author contributions**

421 W.Z and Y.L have conceived the study and developed the methodology. W.Z created the com-
422 putational software and ran the analyses. All authors interpreted the results. W.Z drafted the
423 initial manuscript. H.S.N and Y.L supervised this study and revised the manuscript critically.

424 **8 Disclosures**

425 The authors declare no conflict of interest.

426 **9 Data and Software Availability**

427 SparsePro is an open-access software and publicly available at <https://github.com/zhwm/>
428 SparsePro. All simulation and plotting scripts to reproduce this study are publicly available at
429 https://github.com/zhwm/SparsePro_Paper. Individual-level phenotype and genotype data
430 from the UK Biobank are available upon successful application to its research committee. GCTA

431 were downloaded from https://cnsgenomics.com/software/gcta/bin/gcta_1.93.2beta.zip.
 432 FINEAMP were downloaded from http://www.christianbenner.com/finemap_v1.4_x86_64.tgz. SuSiE (version 0.11.42) were installed from CRAN. PolyFun were installed from <https://github.com/omerwe/polyfun>. UK Biobank LD information was downloaded from https://alkesgroup.broadinstitute.org/UKBB_LD/. Tissue-specific eQTL were obtained from https://storage.googleapis.com/gtex_analysis_v8/single_tissue_qtl_data/GTEx_Analysis_v8_eQTL_EUR.tar.

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SparsePro Supplementary Information

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1 Supplementary Notes

1.1 SparsePro is not sensitive to hyperparameter K

The number of causal effects K is an important hyperparameter in statistical fine-mapping. In methods that exhaustively search through causal configurations, the computation time increases combinatorially with K since the number of candidate causal configurations also grows combinatorially. In contrast, in SparsePro, the computation time increases linearly with K . In practice, most of the computation time is spent on loading LD information, thus the computation time varies only slightly with $K \in \{5, 7, 9, 11\}$. The output of SparsePro is not sensitive to the choice of K as long as K is greater than or equal to the actual number of causal effects. In our simulation studies, we found that with $K = 7, 9$, or 11 , the resulting PIPs were extremely highly correlated with those based on $K = 5$, and the overall AUPRC metrics were also highly consistent (**Supplementary Table S2**).

1.2 Modified HESS estimates for hyperparameters τ_y and τ_β

Local heritability estimates are useful in setting hyperparameters for SparsePro. Shi et al. [32] provided an unbiased estimator for local heritability estimation based on summary statistics:

$$\hat{h}_g = \frac{N\hat{\beta}^T \mathbf{R}^{-1} \hat{\beta} - P}{N - P}$$

where $\mathbf{R}$ is the LD matrix, $\hat{\beta}$ is GWAS summary effect size, N is the sample size in the GWAS and P is the number of SNPs considered in a locus. However, this estimate requires that when generating summary statistics, both genotypes and phenotypes should be standardized to have zero mean and unit variance. Since summary statistics generated by some GWAS pipelines do not specifically standardize the genotypes and phenotypes, we modified the HESS estimator to account for the non-unit variance:

$$\hat{h}_g = \frac{(\hat{\beta} \circ \mathbf{v})^T (\mathbf{X}^T \mathbf{X})^{-1} (\hat{\beta} \circ \mathbf{v}) - \text{var}(\mathbf{y})P}{\text{var}(\mathbf{y})(N - P)}$$

where $\circ$ represents element-wise multiplication and $\mathbf{v}$ is a $P \times 1$ vector: $v_p = \mathbf{X}_p^T \mathbf{X}_p$ for the p -th SNP with genotype vector $\mathbf{X}_p$. This estimate can be adapted to directly operate on summary statistics as explained in **Materials and Methods**.

1.3 Full derivation of variational EM algorithm:

As has been described in **Materials and Methods**, based on the data generative process, for the k -th causal effect, we have:

$$\mathbf{s}_k \sim \text{Multinomial}(1, \tilde{\boldsymbol{\pi}})$$

$$\beta_k \sim \mathcal{N}(0, \tau_{\beta_k}^{-1})$$

$$\mathbf{y} = \mathbf{X} \sum_k \mathbf{s}_k \beta_k + \boldsymbol{\epsilon}$$

559 with $\epsilon_i \sim N(0, \tau_y^{-1})$. Therefore, we have the joint probability:

$$p(\mathbf{y}, \mathbf{S}, \boldsymbol{\beta} | \mathbf{X}, \tilde{\boldsymbol{\pi}}, \tau_\beta, \tau_y) = p(\mathbf{y} | \mathbf{X}, \mathbf{S}, \boldsymbol{\beta}, \tau_y) \prod_k p(\beta_k | \tau_{\beta_k}) \prod_k p(\mathbf{s}_k | \tilde{\boldsymbol{\pi}}) \quad (4)$$

The goal of fine-mapping is to infer the posterior probability, and in particular, of the sparse projection $\mathbf{S}$ (from here we make the dependency on hyperparameters implicit for the ease of notation):

$$p(\mathbf{S}, \boldsymbol{\beta} | \mathbf{y}, \mathbf{X}) = \frac{p(\mathbf{y}, \mathbf{S}, \boldsymbol{\beta} | \mathbf{X})}{p(\mathbf{y} | \mathbf{X})}$$

560 We use a paired mean field factorized [18] variational family $q(\mathbf{S}, \boldsymbol{\beta})$ to approximate the pos-
561 terior:

$$q(\mathbf{S}, \boldsymbol{\beta}) = \prod_k q(\mathbf{s}_k, \beta_k) = \prod_k q(\mathbf{s}_k) q(\beta_k | \mathbf{s}_k)$$

562 Note that in this variational family, we do not specify the form of the distribution; rather, we
563 only specify the dependency of β_k on $\mathbf{s}_k$ and that all K causal effects are independent of each
564 other. Also, the form of the variational family does not depend on any observed data.

565 To better approximate the posterior distribution with members of the variational family, we
566 aim to minimize the KL divergence between the posterior distribution and the proposed varia-
567 tional distribution, which is equivalent to maximizing the ELBO [30]:

$$ELBO = E_{q(\mathbf{S}, \boldsymbol{\beta})}[\log p(\mathbf{y}, \mathbf{S}, \boldsymbol{\beta} | \mathbf{X})] - E_{q(\mathbf{S}, \boldsymbol{\beta})}[\log q(\mathbf{S}, \boldsymbol{\beta})]$$

To maximize the above ELBO, the following requirement should be satisfied for each k :

$$\log q(\mathbf{s}_k, \beta_k) = E_{q(\mathbf{S}_{\setminus k}, \boldsymbol{\beta}_{\setminus k})}[(\mathbf{y}, \mathbf{S}, \boldsymbol{\beta} | \mathbf{X})]$$

where $E_{q(\mathbf{S}_{\setminus k}, \boldsymbol{\beta}_{\setminus k})}$ is the expectation with respect to the variational distribution excluding the k -th

component. With the joint probability provided in Equation (4) we have

$$\begin{aligned}\log p(\mathbf{y}, \mathbf{S}, \boldsymbol{\beta} | \mathbf{X}) &= \log p(\mathbf{y} | \mathbf{X}, \mathbf{S}, \boldsymbol{\beta}) + \sum_k \log p(\beta_k | \tau_{\beta_k}) + \sum_k (\mathbf{s}_k | \tilde{\boldsymbol{\pi}}) \\ &= \frac{N}{2} \log \frac{\tau_y}{2\pi} - \frac{\tau_y}{2} (\mathbf{y} - \mathbf{X}(\sum_k \mathbf{s}_k \beta_k))^\top (\mathbf{y} - \mathbf{X}(\sum_k \mathbf{s}_k \beta_k)) \\ &\quad + \sum_k \left(\frac{1}{2} \log \frac{\tau_{\beta_k}}{2\pi} - \frac{\tau_{\beta_k}}{2} \beta_k^2 \right) + \sum_k \sum_g s_{kg} \log \tilde{\pi}_g\end{aligned}$$

568 Taking expectation with respect to the variational distribution excluding the k -th component
569 and plugging in $s_{kg} = 1$ and $s_{k \setminus g} = 0$ for all SNPs excluding the g -th SNP, we can obtain the joint
570 distribution of the k -th effect as:

$$\log q(s_{kg} = 1, \mathbf{s}_{k \setminus g} = \mathbf{0}, \beta_k) = \text{const} - \frac{\tau_{\beta_k}}{2} \beta_k^2 - \frac{\tau_y}{2} \mathbf{X}_g^\top \mathbf{X}_g \beta_k^2 + \tau_y \beta_k \mathbf{X}_g^\top (\mathbf{y} - X \tilde{\boldsymbol{\beta}}_{\setminus k}) + \log \tilde{\pi}_g \quad (5)$$

571 where

$$\tilde{\boldsymbol{\beta}}_{\setminus k} = E_{q(\mathbf{s}_{\setminus k}, \boldsymbol{\beta}_{\setminus k})} \left[\sum_{k' \neq k} \mathbf{s}_{k'} \beta_{k'} \right] = \sum_{k' \neq k} \gamma_{k'}^* \circ \mu_{k'}^*$$

572 We recognize that

$$q(\beta_k | s_{kg}=1, \mathbf{s}_{k \setminus g} = \mathbf{0}) \sim \mathcal{N}(\mu_{kg}^*, \tau_{kg}^*)$$

By matching sufficient statistics for this normal distribution, we can obtain the following variational parameters for updates:

$$\begin{aligned}\tau_{kg}^* &= \tau_y \mathbf{X}_g^\top \mathbf{X}_g + \tau_{\beta_k} \\ \mu_{kg}^* &= \frac{\tau_y}{\tau_{kg}^*} \mathbf{X}_g^\top (\mathbf{y} - X \tilde{\boldsymbol{\beta}}_{\setminus k})\end{aligned}$$

By integrating out β_k in Equation (5), we obtain that

$$\log q(s_{kg} = 1, \mathbf{s}_{k \setminus g} = \mathbf{0}) = \log \tilde{\pi}_g - \frac{1}{2} \log \frac{\tau_{kg}^*}{2\pi} + \frac{1}{2} \tau_{kg}^* \mu_{kg}^{*2} + \text{const}$$

Therefore, the posterior probability of the g -th SNP being causal in the k -th effect can be estimated as:

$$\gamma_{kg}^* := q(s_{kg} = 1, \mathbf{s}_{k \setminus g} = \mathbf{0}) = \text{softmax}(\log \tilde{\pi}_g - \frac{1}{2} \log \frac{\tau_{kg}^*}{2\pi} + \frac{1}{2} \tau_{kg}^* \mu_{kg}^{*2})$$

This completes the variational expectation step in our inference algorithm. When functional annotations are available, we use the following maximization step to integrate relevant annotations. After the expectation step, we have that

$$\begin{aligned} ELBO &= \text{const} + \sum_{k,g} \gamma_{k,g}^* \log \tilde{\pi}_g \\ &= \text{const} + \sum_{k,g} \gamma_{k,g}^* \log \frac{\exp(\mathbf{A}_g \mathbf{w})}{\sum_g \exp(\mathbf{A}_g \mathbf{w})} \\ &= \text{const} + \sum_{k,g} \gamma_{k,g}^* [\mathbf{A}_g \mathbf{w} - \log(\sum_g \exp(\mathbf{A}_g \mathbf{w}))] \end{aligned}$$

To maximize ELBO with respect to the relative enrichment of the m -th candidate annotation,

we take partial derivatives of ELBO with respect to w_m and set it to 0 to solve for w_m :

$$\begin{aligned}
\frac{\partial ELBO}{\partial w_m} &= \sum_{k,g} \gamma_{k,g}^* [A_{gm} - \frac{\sum_g A_{gm} \exp(\mathbf{A}_g \mathbf{w})}{\sum_g \exp(\mathbf{A}_g \mathbf{w})}] \\
&= \sum_{k,g} \gamma_{k,g}^* [A_{gm} - \frac{\sum_g A_{gm} \exp(A_{gm} w_m) \exp(\sum_{m' \neq m} A_{gm'} w_{m'})}{\sum_g \exp(A_{gm} w_m) \exp(\sum_{m' \neq m} A_{gm'} w_{m'})}] \\
&= \sum_{k,g} \gamma_{k,g}^* [A_{gm} - \frac{\sum_g A_{gm} \exp(A_{gm} w_m) \text{softmax}(\sum_{m' \neq m} A_{gm'} w_{m'})}{\sum_g \exp(A_{gm} w_m) \text{softmax}(\sum_{m' \neq m} A_{gm'} w_{m'})}] \\
&= \sum_{k,g} [A_{gm} = 1] \gamma_{kg}^* \\
&\quad - \sum_{k,g} \gamma_{kg}^* \frac{e^{w_m} \sum_g [A_{gm} = 1] \text{softmax}(\sum_{m' \neq m} A_{gm'} w_{m'})}{e^{w_m} \sum_g [A_{gm} = 1] \text{softmax}(\sum_{m' \neq m} A_{gm'} w_{m'}) + \sum_g [A_{gm} = 0] \text{softmax}(\sum_{m' \neq m} A_{gm'} w_{m'})} \\
&= r_1 - (r_1 + r_0) \frac{k_1 e^{w_m}}{k_1 e^{w_m} + k_0} \\
&= 0
\end{aligned}$$

where

$$\begin{aligned}
k_1 &= \sum_g [A_{gm} = 1] \text{softmax}(\sum_{m' \neq m} A_{gm'} w_{m'}) \\
k_0 &= \sum_g [A_{gm} = 0] \text{softmax}(\sum_{m' \neq m} A_{gm'} w_{m'}) \\
r_1 &= \sum_{k,g} [A_{gm} = 1] \gamma_{kg}^* \\
r_0 &= \sum_{k,g} [A_{gm} = 0] \gamma_{kg}^*
\end{aligned}$$

We then obtain:

$$\frac{k_1 e^{w_m}}{k_1 e^{w_m} + k_0} = \frac{r_1}{r_1 + r_0}$$

and solve for:

$$w_m = \log \left(\frac{r_1/r_0}{k_1/k_0} \right)$$

574 Notably, this estimate is analogous to a relative risk estimate in a 2×2 contingency table. Sup-
 575 pose we consider one annotation, then k_1 corresponds to the number of variants with this spe-
 576 cific annotation while k_0 corresponds to the number of variants without the annotation. Mean-
 577 while, r_0 corresponds to the sum of posterior probability for variants with the annotation while r_1
 578 corresponds to the sum of posterior probability for variants without the annotation.

Similarly, the standard error of this estimate can be calculated based on the standard error of
 a relative risk:

$$se(\hat{w}_m) = \sqrt{\frac{1}{r_1} + \frac{1}{r_0} - \frac{1}{k_1} - \frac{1}{k_0}}$$

579 Finally, we can evaluate the statistical significance of enrichment with the log likelihood ratio
 580 test (G-test) [31].

581 2 Supplementary Table Legends

582 **Supplementary Table S1** Relative enrichment of functional priors in simulation studies.

583 **Supplementary Table S2** Comparison of fine-mapping results based on different hyperpa-
 584 rameter settings of the number of causal effects K .

585 **Supplementary Table S3** Details of computation time by each method.

586 **Supplementary Table S4** Fine-mapping results for five functional biomarkers based on the
 587 UK Biobank, including genetic variants with a PIP > 0.1 .

588 **Supplementary Table S5** Relative enrichment of functional annotations for five functional
589 biomarkers.

590 **Supplementary Table S6** Comparison of fine-mapped SNP heritability for five functional
591 biomarkers.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TableS1.xlsx](#)
- [TableS2.xlsx](#)
- [TableS3.xlsx](#)
- [TableS4.xlsx](#)
- [TableS5.xlsx](#)
- [TableS6.xlsx](#)