This approximation achieves a favorable balance between computational efficiency and inferential accuracy, enabling scalable application to genome-wide datasets and multi-trait analyses.

3.2 Methodological features: information integration, scalability, and resolution

From a methodological perspective, the strengths of fastPAINTOR are first reflected in its ability to directly incorporate external functional information into the modeling of causal probabilities. Variants located in enhancer or promoter regions, or supported by eQTL evidence, are assigned higher prior weights by the model. As a result, the posterior inclusion probability (PIP) reflects not only the strength of statistical association, but also signals of functional relevance, thereby giving candidate causal variants greater biological interpretability (Kichaev et al., 2016).

At the same time, fastPAINTOR also shows strong scalability at the computational level. By adopting approximate Bayesian inference, the method avoids the computational bottleneck of MCMC in high-dimensional causal configuration spaces, allowing it to maintain relatively high efficiency under large-scale GWAS data and multiple annotation settings. This property is particularly important for current large-sample studies represented by biobank-scale datasets.

On this basis, the incorporation of functional annotations can further improve the resolution of causal localization. In particular, under multi-trait or multi-annotation settings, fastPAINTOR can often effectively reduce the size of the credible set. Previous studies have shown that, while maintaining relatively high coverage, the inclusion of functional annotations can reduce the candidate set by approximately 40%~60% (Kichaev et al., 2016). For studies in which downstream experimental validation resources are limited, such compression of the candidate space has direct practical value.

When these features are considered within a unified framework, the main advantage of fastPAINTOR can be understood as arising from the optimization of prior structure. In other words, when the likelihood model remains unchanged, the introduction of functional annotations improves the identifiability of the causal probability distribution, thereby enhancing the model’s ability to distinguish true causal variants.

3.3 Model limitations and sources of bias

Although fastPAINTOR has clear advantages in information integration and computational efficiency, its inferential performance also depends heavily on the validity of the prior model itself. As a result, while this method improves interpretability, it also introduces new methodological risks.

3.3.1 Prior misspecification

When functional annotations are noisy, incomplete, or biased, the prior distribution may distort posterior inference, leading to over-prioritization of non-causal variants or underestimation of true causal variants. This issue can be viewed as a prior-induced shift in the causal estimand and may require mitigation through multi-annotation integration or sensitivity analyses.

3.3.2 Limited transferability across populations

Functional annotations are often tissue-specific or population-specific. In cross-ancestry studies or non-model organisms, annotation information may not generalize, potentially reducing model performance. Consequently, interpretation of results in such contexts should be approached with caution.

3.3.3 Approximation error

While variational inference improves scalability, it may underestimate posterior uncertainty in regions with complex LD structure or multiple causal variants. This can result in overly compact credible sets or the omission of true causal variants.