Bayesian posterior estimation of Gene Regulatory Networks from Zero-Inflated Single-Cell Data

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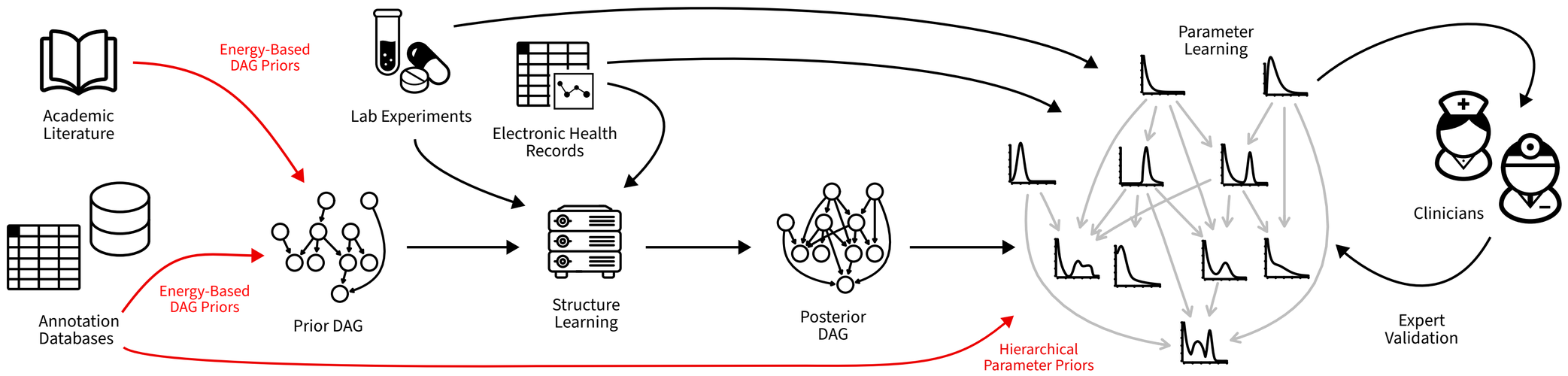
Informative Priors to Augment Molecular Network Learning



Energy-Based Priors & Structure Learning

KEGG, DoRothEA and other annotation databases [1] contain enough information to build an *a priori* DAG $\mathcal{G}_0$ to prime gene regulatory network learning. With energy-based priors [2], the energy function

$$E(\mathcal{G}, \mathcal{G}_0; w) = w\widetilde{\text{SHD}}(\mathcal{G}, \mathcal{G}_0) + (1-w)\widetilde{\text{SID}}(\mathcal{G}, \mathcal{G}_0), \quad w \in [0,1]$$

and the associated graphical prior

$$\text{P}(\mathcal{G}; \mathcal{G}_0, \beta, w) = \exp\left\{-\beta E(\mathcal{G}, \mathcal{G}_0; w)\right\}, \qquad \beta \geqslant 0,$$

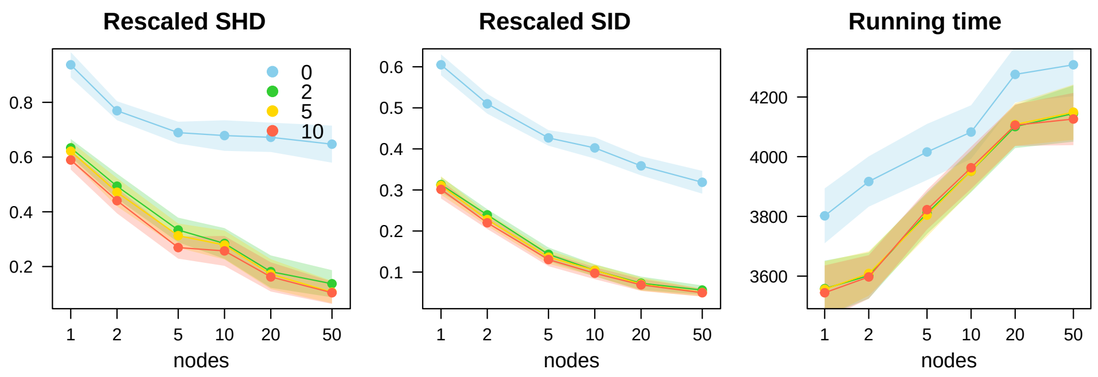
encourage both local (SHD) and global (SID) consistency.

- Structural Hamming Distance ($\widetilde{\text{SHD}}$, scaled [3]): individual-arc differences in presence and direction.
- Structural Interventional Distance (SID, scaled [4]): discrepancies along causal pathways after interventions (say, knock-outs).

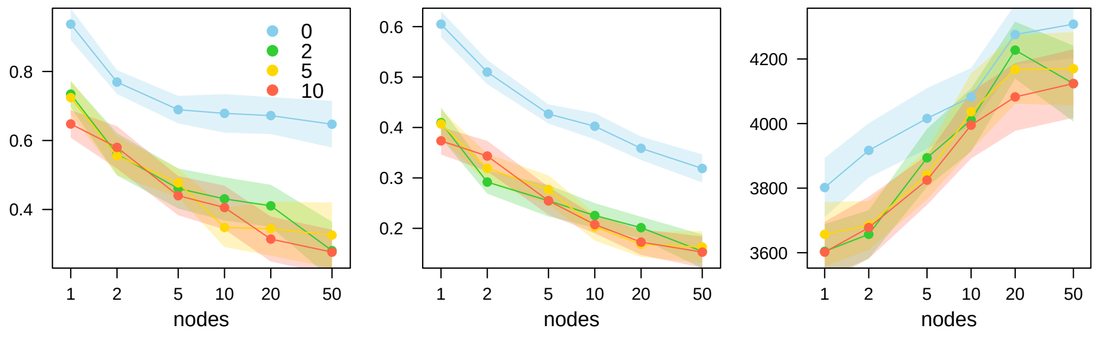
Practical Performance

Benchmarked with the gene expression (ECOLI70) and SNP + phenotype (MAGIC-NIAB, MAGIC-IRRI) reference networks [5].

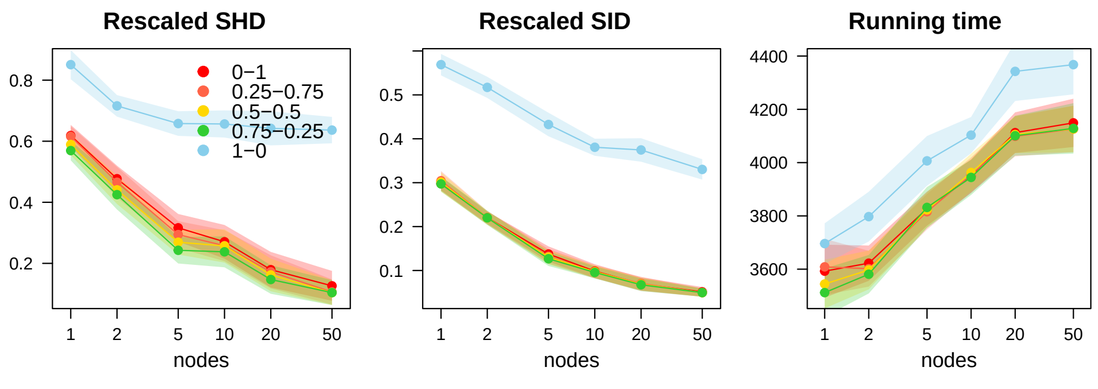
- More accurate and faster ($\beta > 0$) than baseline ($\beta = 0$).



- Robust against even to 20% incorrect arcs in $\mathcal{G}_0$.



- Not sensitive to the choice of w as long as $w < 1$ (here $\beta = 10$).



Zero-Inflated DAGs

Zero-inflated generalised hypergeometric (GHP) DAGs [ZiG-DAG; 6],

$$\text{P}(X_i \mid \text{pa}(X_i)) = \begin{cases} \pi_i + (1-\pi_i)\text{GHP}(X_i, \lambda_i) & \text{(structural zeros)} \\ (1-\pi_i)\text{GHP}(X_i, \lambda_i) & \text{(pseudocounts)} \end{cases},$$

$\pi_i = \pi(\text{pa}(X_i)), \lambda_i = \lambda(\text{pa}(X_i))$, allow causal identifiability, but:

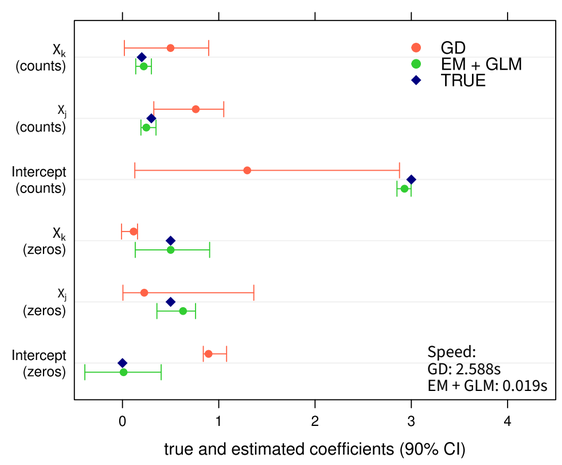
- estimating both components simultaneously by gradient descent is numerically unstable.
- estimating the parameters independently for each $X_i \mid pa(X_i)$ disregards pathway status (active/inactive).

Hierarchical, Stable Parameter Estimation

EM + GLM parameter estimation [7] beats gradient descent even in $X_i \mid \text{pa}(X_i)$ with few parameters and large samples.

1. *E-Step:* Estimate the structural zero indicators.
2. *M-Step:* Estimate the coefficients of
   - the logistic regression modelling the zero-inflation probability;
   - the GLM modelling the pseudocounts.

Consider:



$X_i \sim ZiPois(\pi_i, \lambda_i)$ with $\text{pa}(X_i) = \{X_j, X_k\}$ and:

$$\text{logit}(\pi_i) = 0.5X_j + 0.5X_k$$
$$\log(\lambda_i) = 3 + 0.3X_j + 0.2X_k$$

200 replicates, random samples with $n = 200$.

Estimates can improve even further with a hierarchical prior that uses the hierarchical grouping of regulatory network nodes (TODO).

References

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