Assessment of Gene Regulatory Network Inference Algorithms Using Monte Carlo Simulations

CCBCOL V

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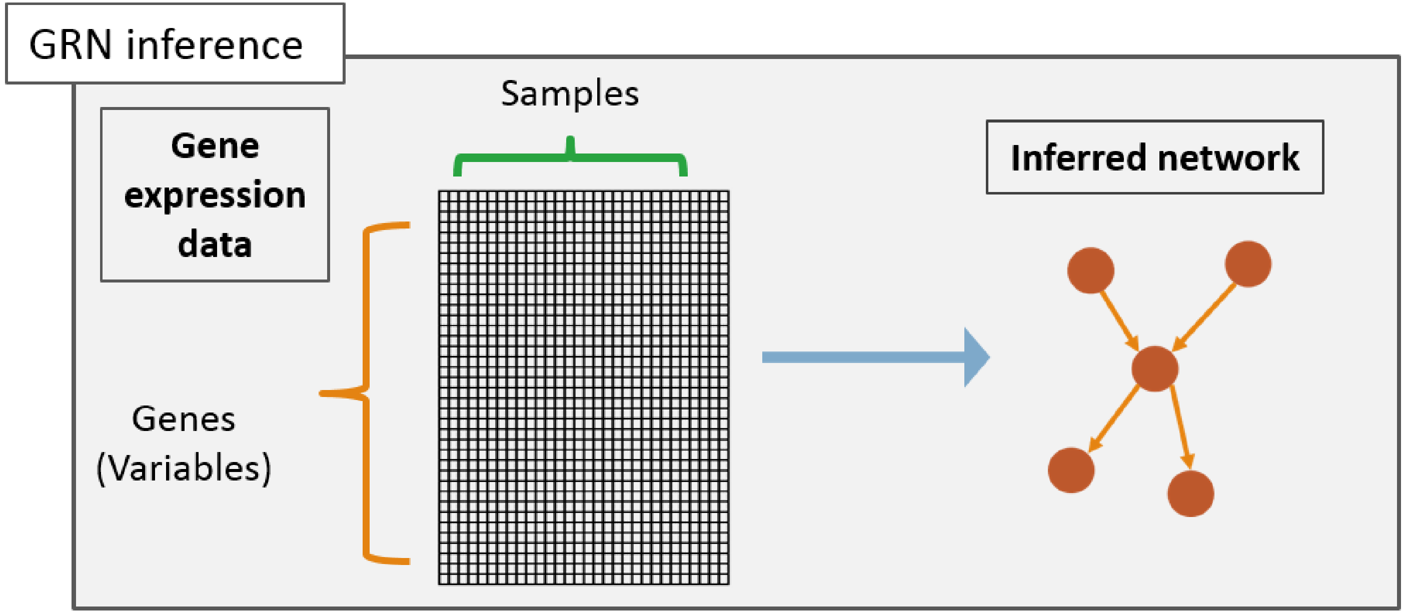
The Theoretical Problem

In bioinformatics there are many methods to build GRNs from gene expression data.



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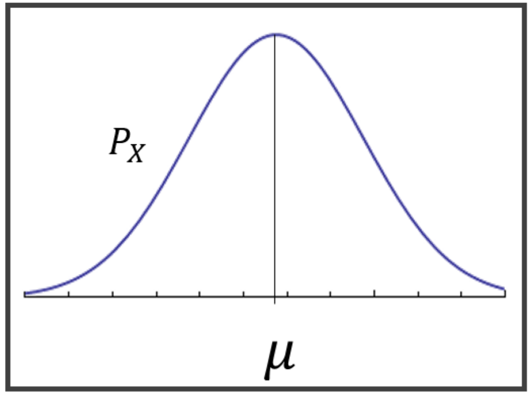
Our question is *do they work well in theory?*

- How dependent is a method on shape of regulatory relations, sample size, noise, etc.?
- How reliable is the method? Are reported results flukes?

Statistics 101

A basic example of statistical inference. We have:

$P_X(x)$	A theoretical model with a probability distribution
$E(X) = \mu$	An unknown parameter of the model to be estimated
$X_1, X_2, \ldots, X_n$ i.i.d. $P_X(x)$	A sample from the distribution
$\overline{X_n}$	A statistic to estimate the parameter of interest



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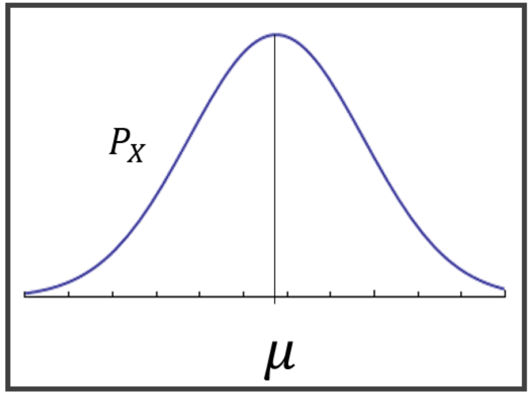

We ask: **is our statistic a good (reliable, accurate) estimator of our parameter?**

- Basic probability says $\bar{X}_n$ is accurate on average.
- By the Law of Large Numbers, $\bar{X}_n$ is increasingly reliable as $n \to \infty$.

The Probabilistic Model

Consider GRN inference algorithms as estimators and look at their statistical properties (unfair).

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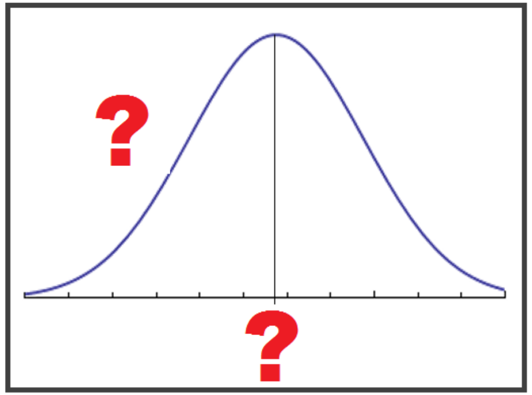
✓ A statistic to estimate the parameter of interest



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Causal Structural Equations Model (SEM)

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\begin{aligned}
X_1 &= \epsilon_1 \\
X_2 &= \epsilon_2 \\
X_3 &= f_3(X_1, X_2, \epsilon_3) \\
X_4 &= f_4(X_3, \epsilon_4) \\
X_5 &= f_5(X_3, \epsilon_5)
\end{aligned}
$$

Each equation is a causal mechanism.

The joint distribution of noise variables ϵ_i determines a joint distribution of gene expressions. This is $P_X(x)$.

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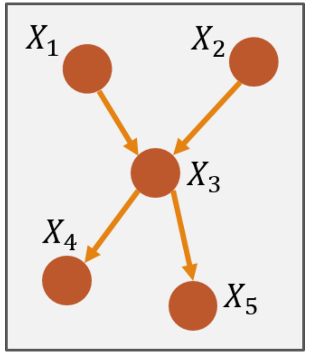
Bayesian Network



Draw edges from direct causes to effects. This is a Bayesian Network, **our parameter of interest**.

Methods We Study

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Mutual information-based

Measure edge stregth by mutual information,

$$I(X_i, X_j) = E\left(\log \frac{f_{X_i}(X_i) f_{X_j}(X_j)}{f_{X_i X_j}(X_i, X_j)}\right).$$

Estimate mutual information with Miller-Madow estimator. Refine/threshold.

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Regression-based

Measure edge strength with scores derived from fitting regressions.

Mutual information-based methods

Mutual information network

Estimate mutual information matrix, threshold.

ARACNe

For each triplet of variables, eliminate edge with lowest estimated MI.

MRNET

Derive 'minimum redundancy, maximum relevance' score from estimated MI.

CLR

Standardize estimated MI matrix row-wise and column-wise. Average both scores.

Regression-based methods

NARROMI

Estimate LAD-Lasso regressions. Use β as scores for edges.

TIGRESS

Estimate Least Angle Regressions (LARS) in a bootstrap (of sorts). Use estimates to compute scores of relevance in prediction.

GENIE3

Estimate an ensembles of regression trees (e.g. random forest). Use estimates to compute scores of relevance in prediction.

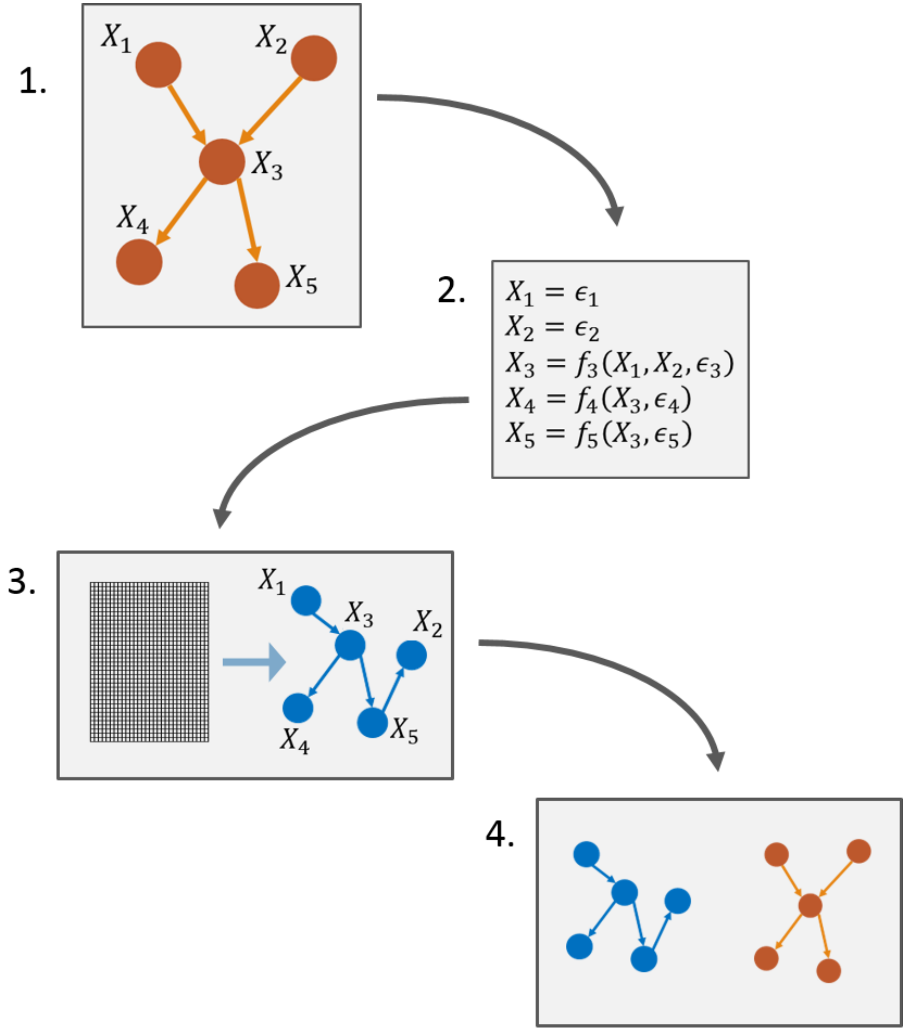
Workflow

1. Fix theoretical network.

2. Generate causal SEMs over this network.

3. Simulate data and apply algorithms.

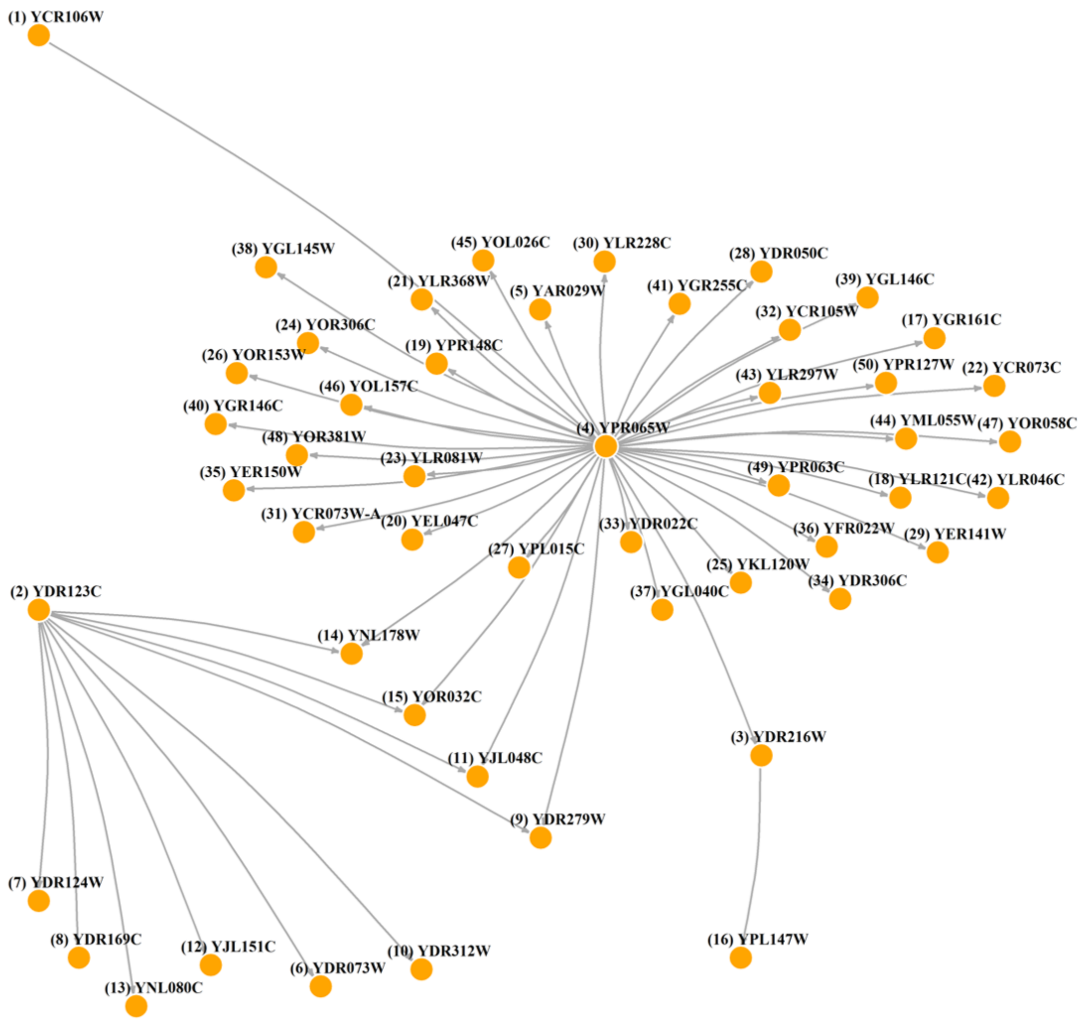
4. Evaluate algorithm outputs.



Sub-network

Source Network: Sisi Ma *et al.* (2014)

Extraction Algorithm: Marbach *et al.* (2009)



Causal SEM Definition

- Linear functional form

$$f_i\left(pa\left(X_i\right), \varepsilon_i\right) = \sum_{X_j \in pa(X_i)} \alpha_{ij} X_j + \varepsilon_i$$

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- Low and high levels of noise

$$FVU_i = \frac{Var(\varepsilon_i)}{Var(X_i)} = 0.2$$

$$FVU_i = \frac{Var(\varepsilon_i)}{Var(X_i)} = 0.8$$

Simulations

- For each causal SEM we simulate 1000 datasets of size 20, 50, 100, and 500.

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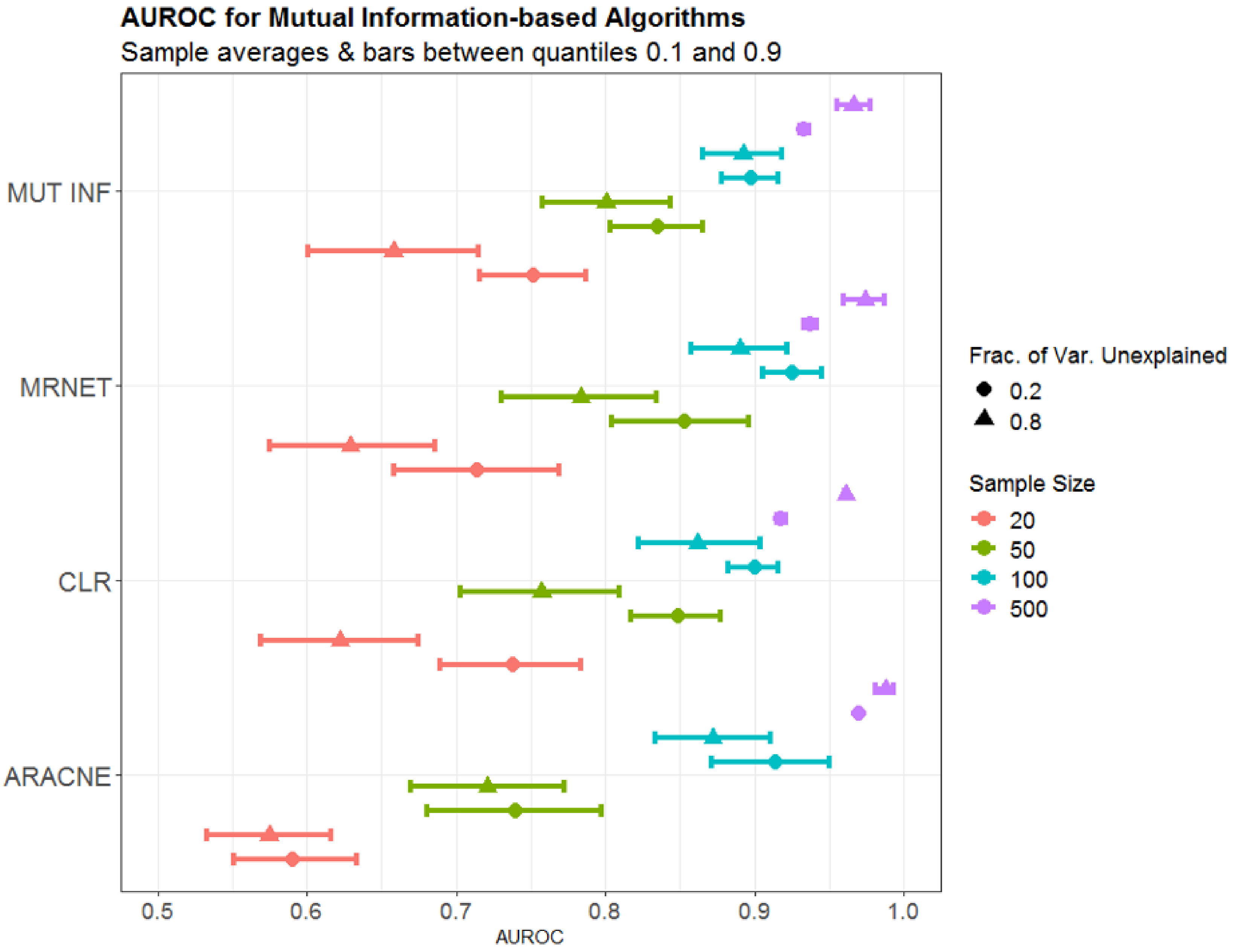
- Algorithms are used "out-of-the-box", that is, using tuning parameters suggested by authors.

Results


AUROC for Mutual Information-based Algorithms
Sample averages & bars between quantiles 0.1 and 0.9
MUT INF
MRNET
CLR
ARACNE
0.5
0.6
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1.0
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Frac. of Var. Unexplained
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20
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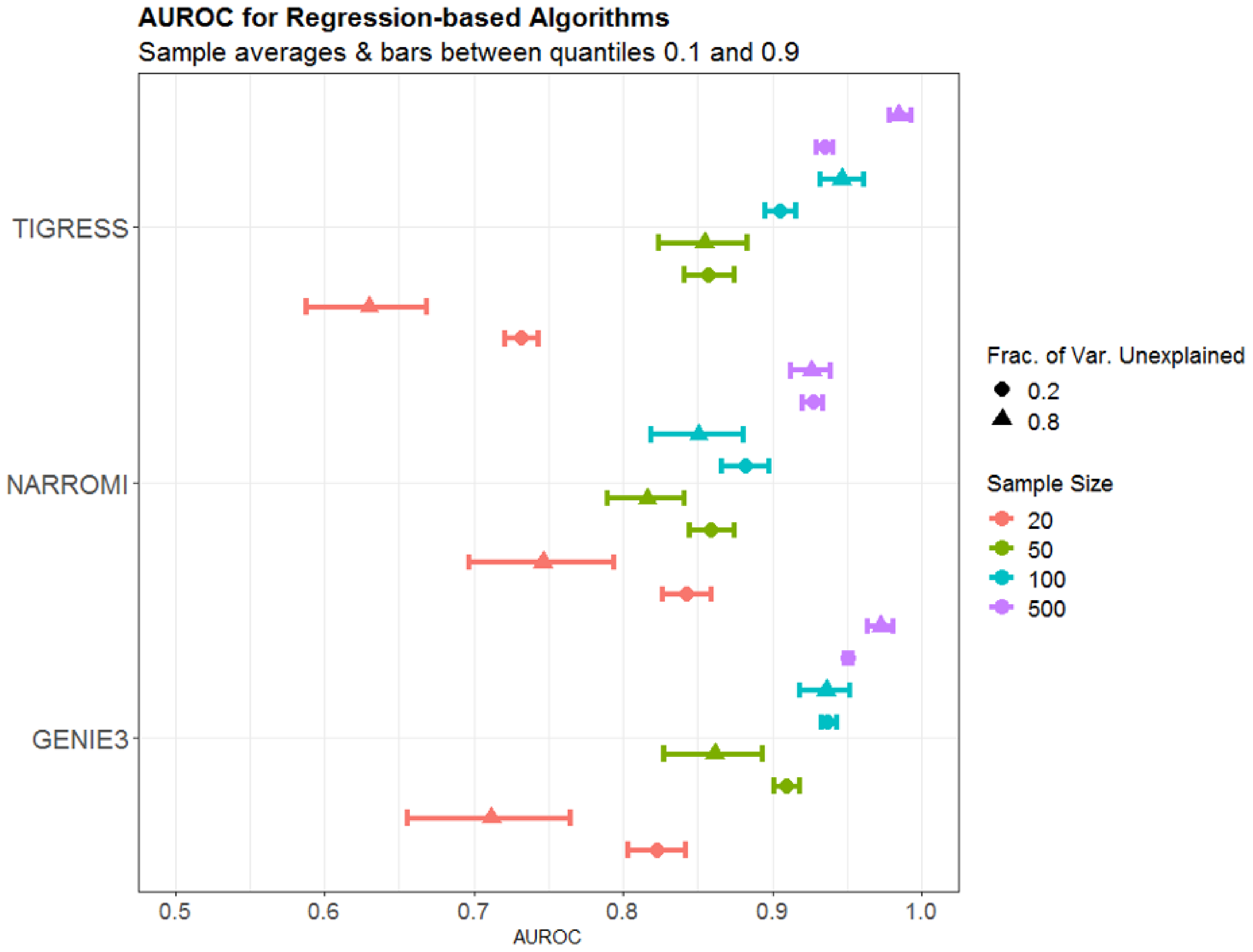

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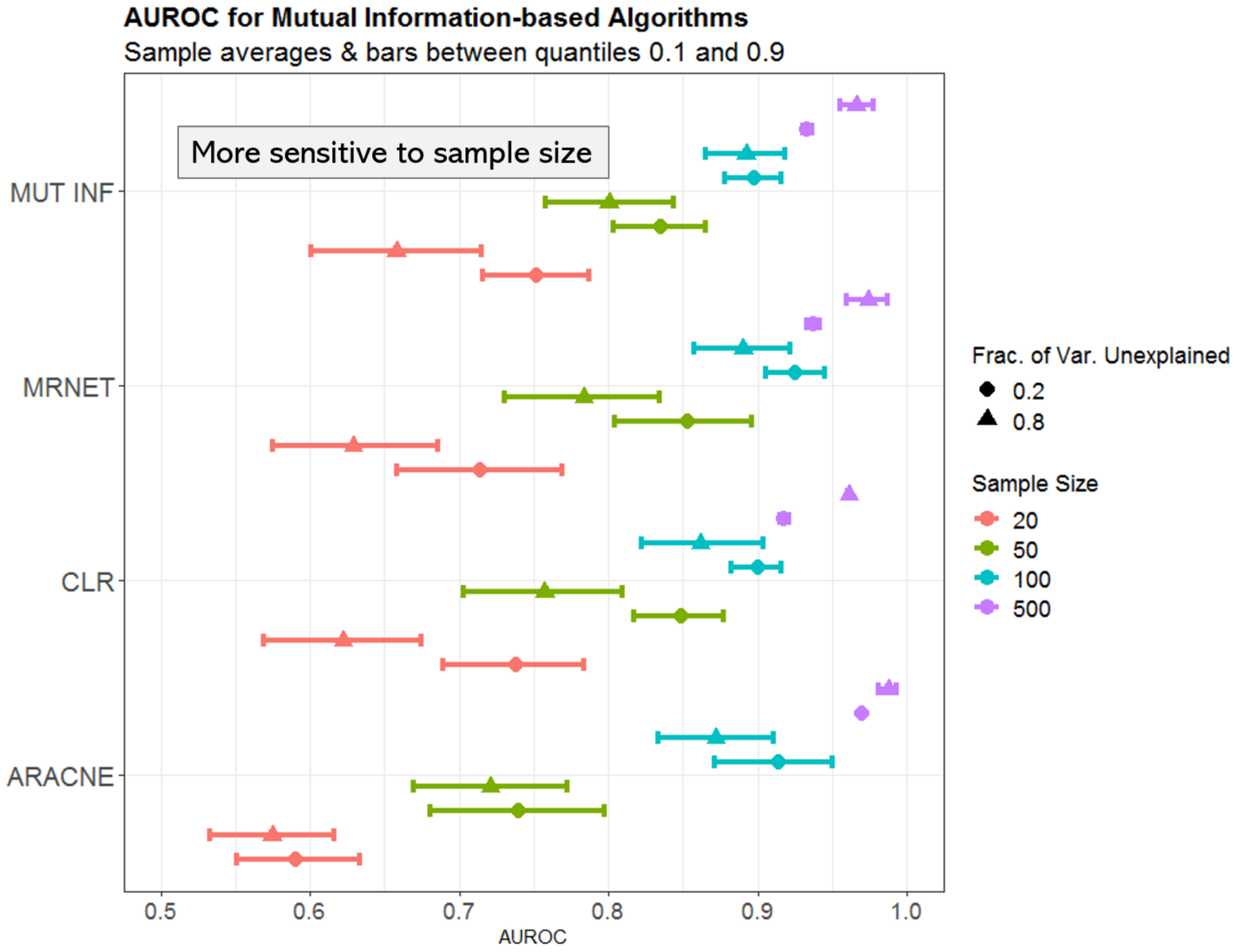

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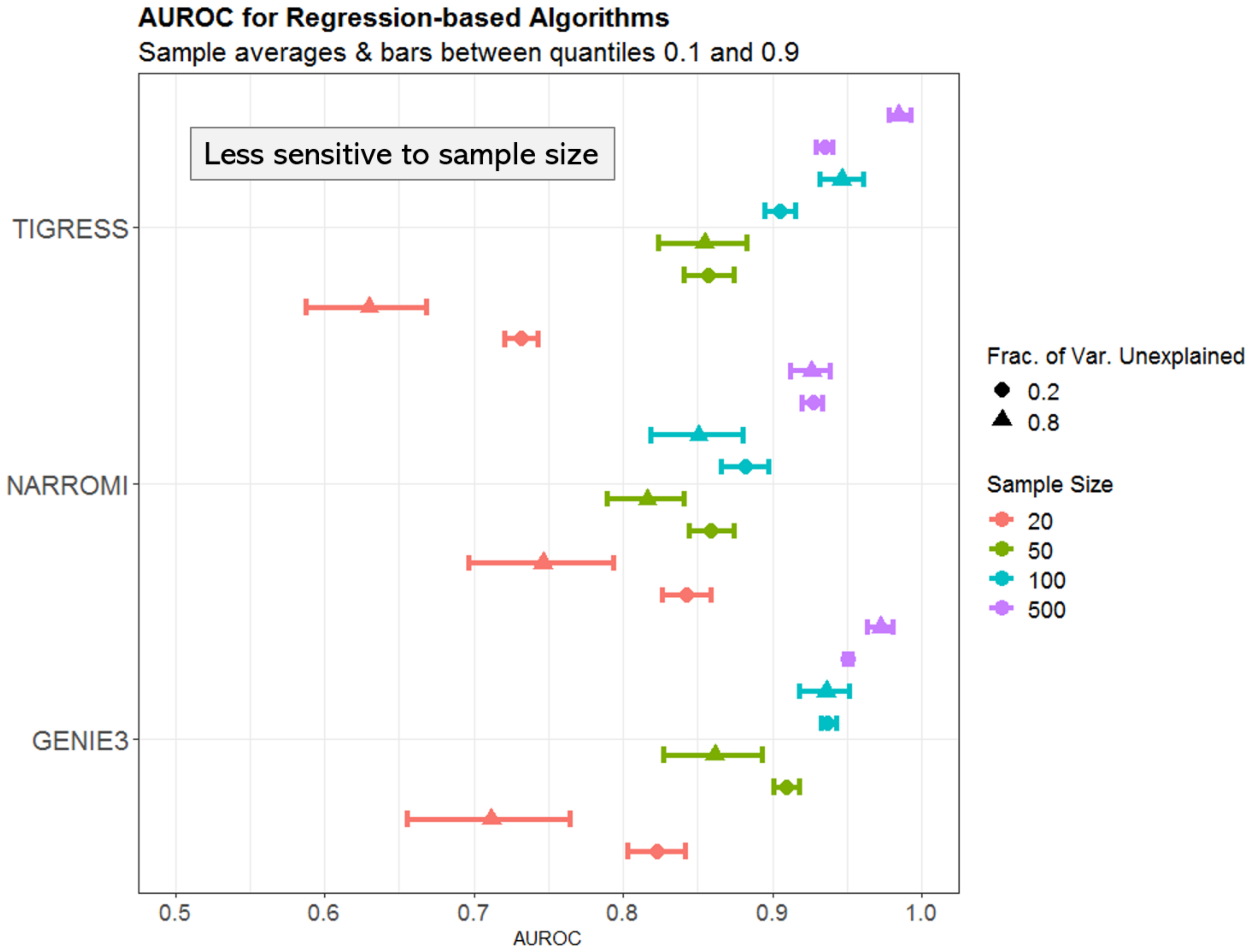
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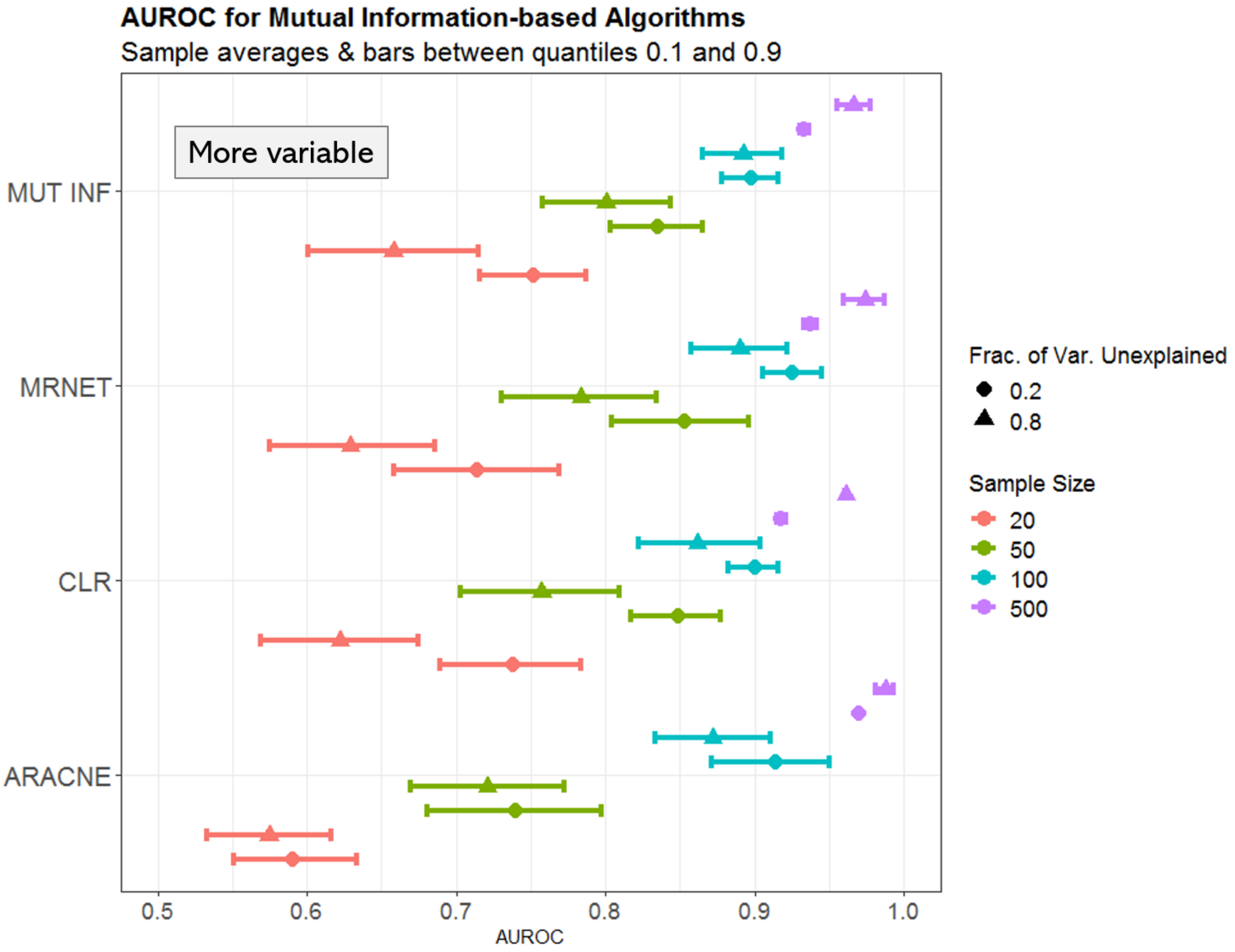

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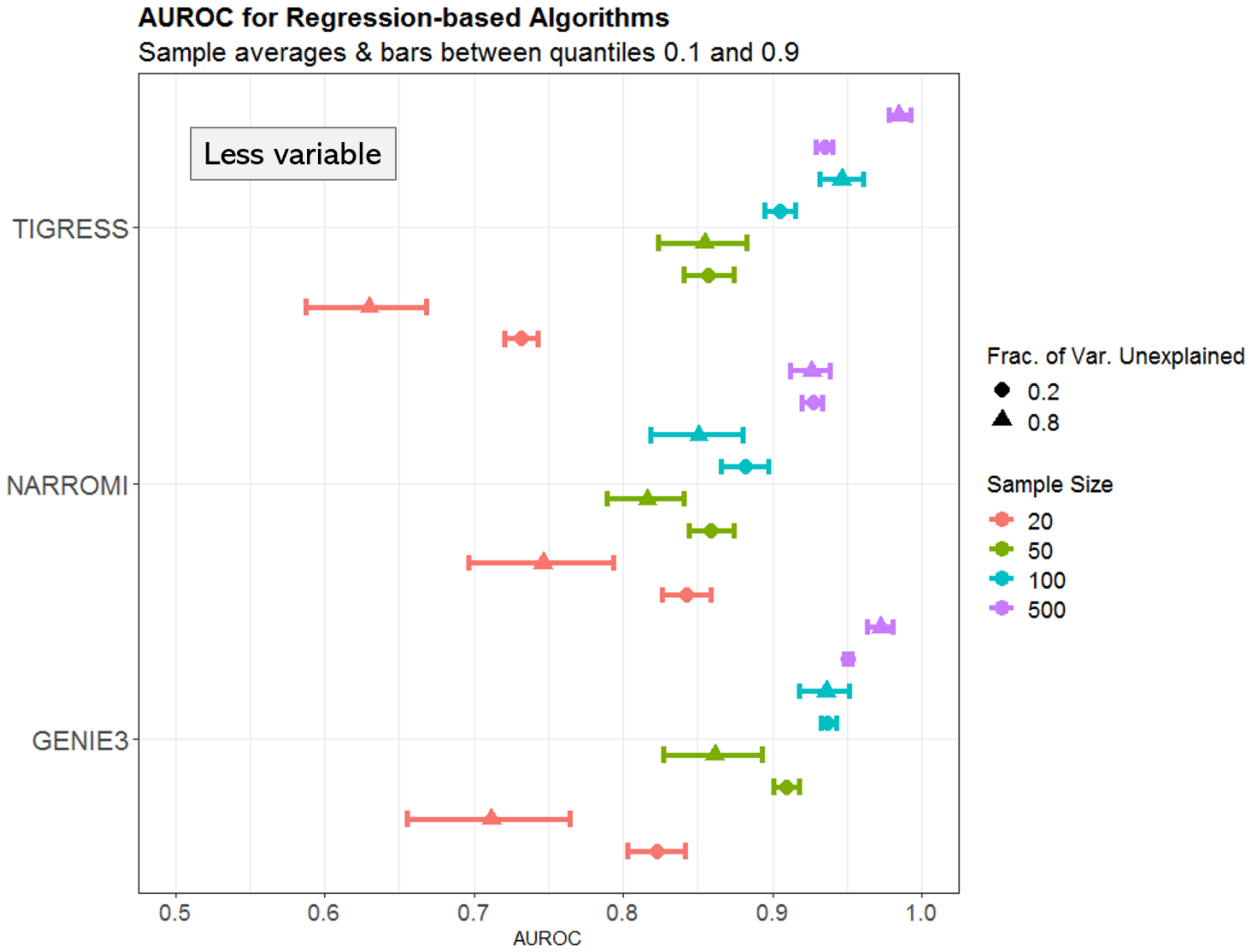

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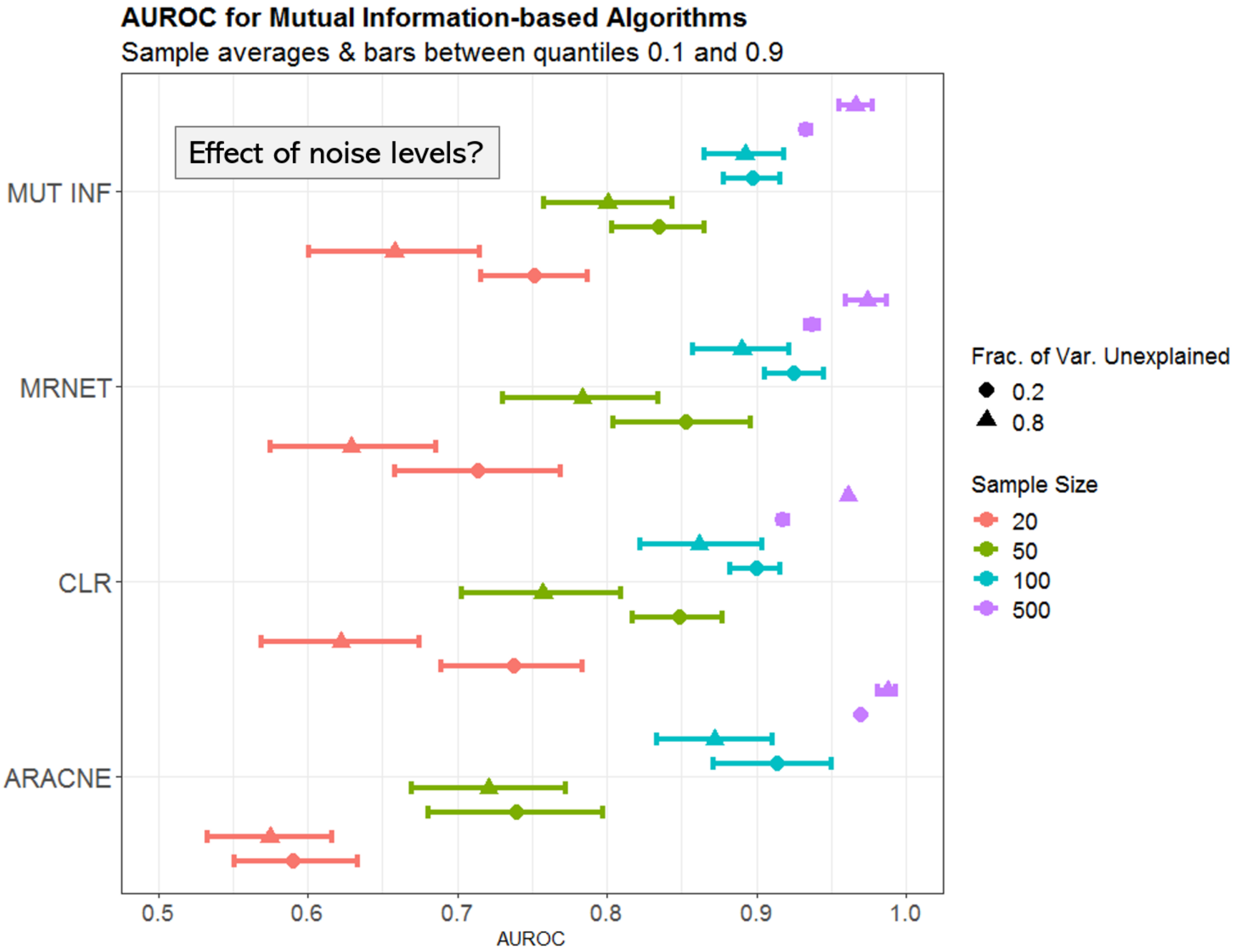
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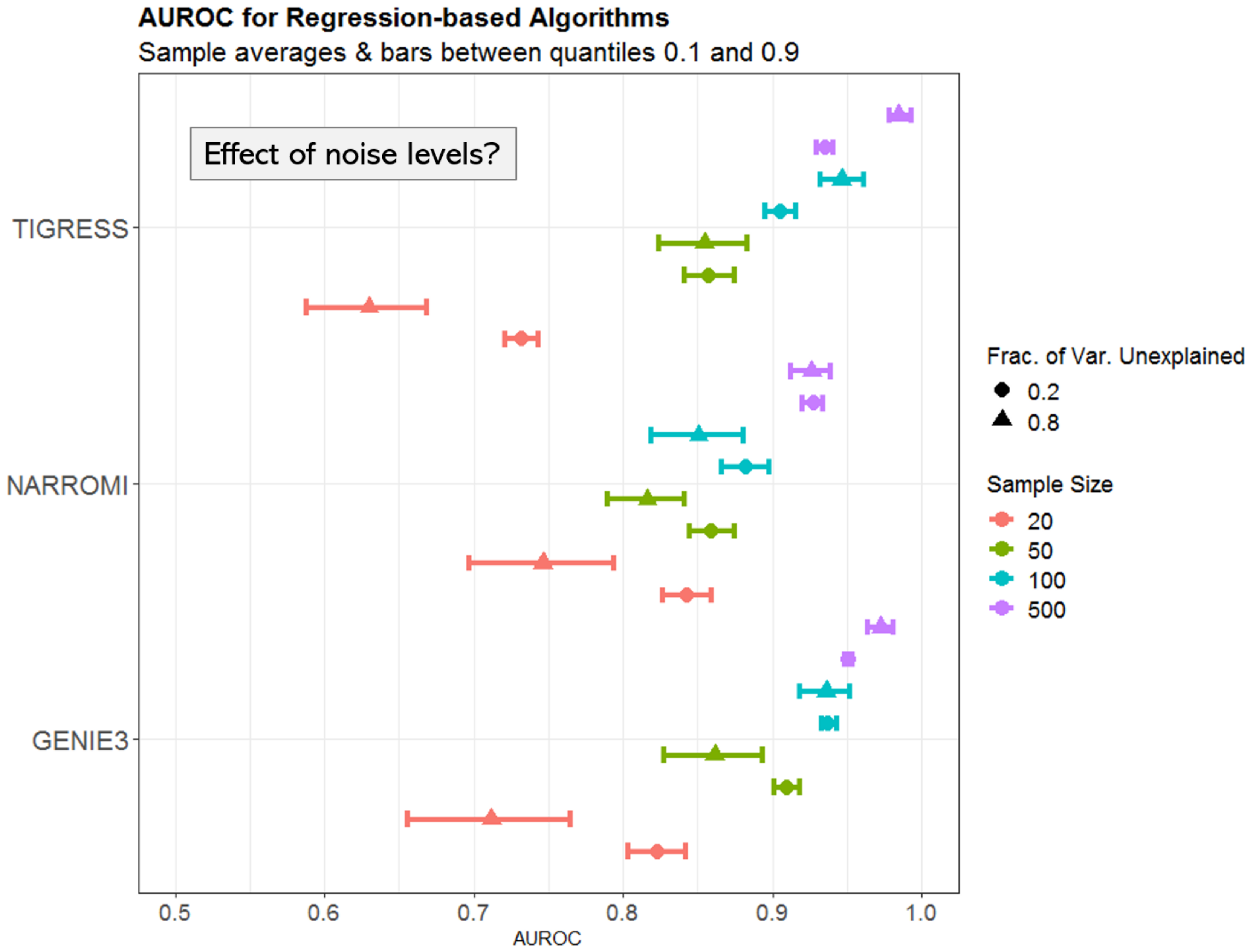

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Thanks

Thanks.

I'm interested in comments or suggestions.

My email is agzuurp@unal.edu.co, and we can talk outside.

References

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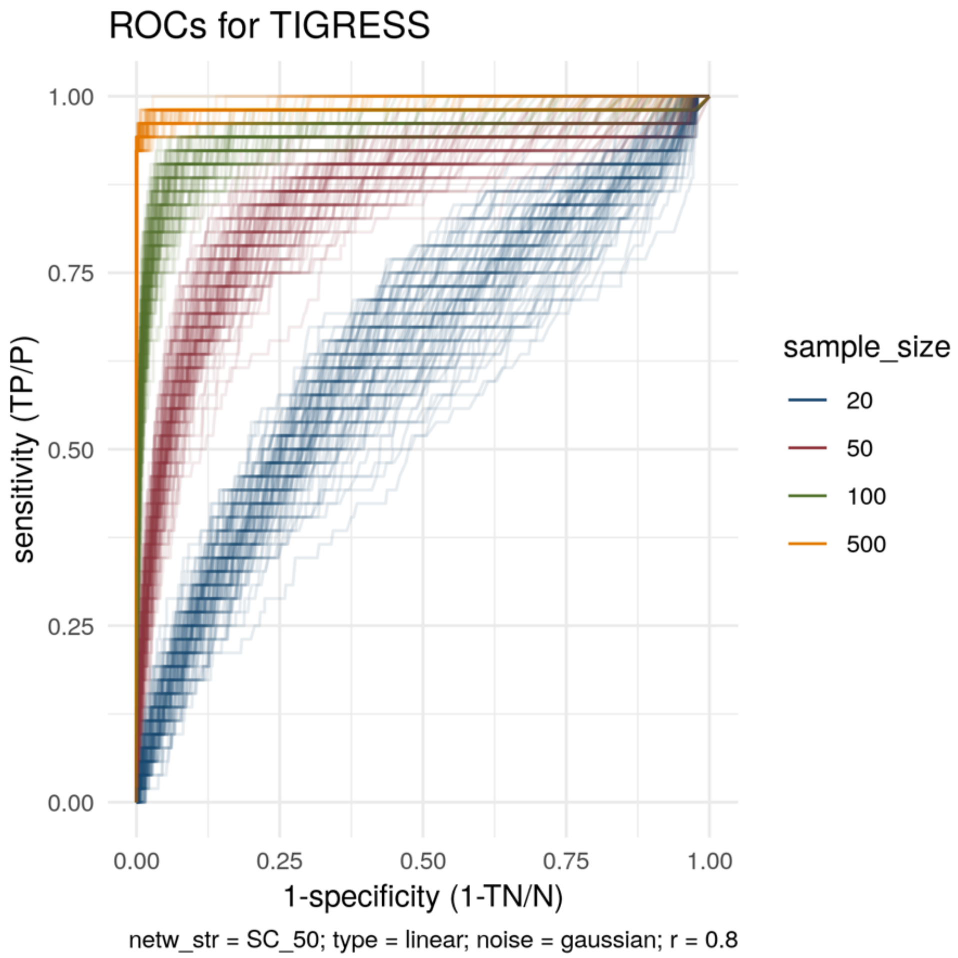
Assessment of Estimates

Each algorithm can be seen as a classifier that outputs scores s_{ij} for edges. For each threshold on scores we get

$$\text{Sensitivity} = \frac{\text{No. of correctly detected edges}}{\text{No. of true edges}}$$

$$\text{Specificity} = \frac{\text{No. of correctly detected non-edges}}{\text{No. of true non-edges}}$$

Over all thresholds, we get a parametric curve - the ROC curve. The area under it, AUROC, is the probability that a randomly sampled true edge has a score higher than that of a randomly sampled non-edge.



- Mutual information was estimated with Miller-Madow estimator.

$$\hat{H}(X) = -\sum_{b_X \in \mathrm{bins}_X} \hat{p}_{b_X} \log\left(\hat{p}_{b_X}\right)$$

$$\hat{H}(Y) = -\sum_{b_Y \in \mathrm{bins}_Y} \hat{p}_{b_Y} \log\left(\hat{p}_{b_Y}\right)$$

$$H(\hat{X}, Y) = -\sum_{b_{X\times Y} \in \mathrm{bins}_{X\times Y}} \hat{p}_{b_{X\times Y}} \log\left(\hat{p}_{b_{X\times Y}}\right)$$

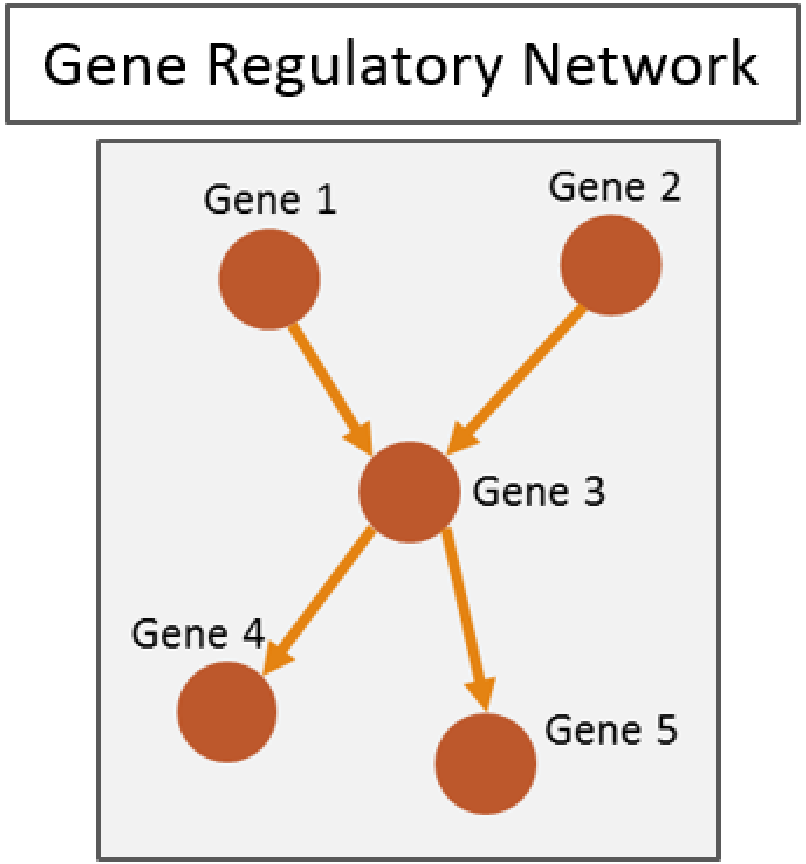
$$\hat{I}(X, Y) = \hat{H}(X) + \hat{H}(Y) - \hat{H}(X, Y) + \frac{\hat{m} - 1}{n}$$

The Scientific Model

Gene regulatory networks (GRNs) are models that aim to encode the regulatory relations among genes in a genome.

- Genes are nodes, regulatory relations are edges.
- Regulatory relations are *causal* (edges are directed, indicate more than co-expression).
- Edges represent *direct* causal effects (indirect effects are directed paths).

GRNs are directed graphs (V, E), which are equivalent to an adjacency matrix.



$$\hat{\beta} = \textbf{argmin}_{\beta \in \mathbb{R}^p} |Y - \beta^\top X| + \lambda ||\beta||_1$$

Results

- MI-based algorithms are more variable than regression-based algorithms.
- MI-based algorithms are more sensitive to sample size than regression-based algorithms. ARACNe and NARROMI are the extremes.
- TIGRESS is most sensitive to FVU. ARACNe is least sensitive.
- Surprisingly good results for large n. Not so much for small n.
- Better results with less noise, except at large sample size. Bias-variance trade-off.