Systematically validated inference of quantitative regulatory networks and condition-specific TF activity

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Transcription factor activity inference

- Quantitative regulatory networks indicate the regulatory potential of TFs on their target genes
- Transcription factor activity (TFA) is the extent to which a TF is exerting its regulatory potential
- Many signals in biological systems are ultimately transduced by TFs, thus they are key to modeling gene regulation and predicting gene expression
- How might we quantitatively evaluate inferred regulatory networks and TFA?

Signed binary starting networks

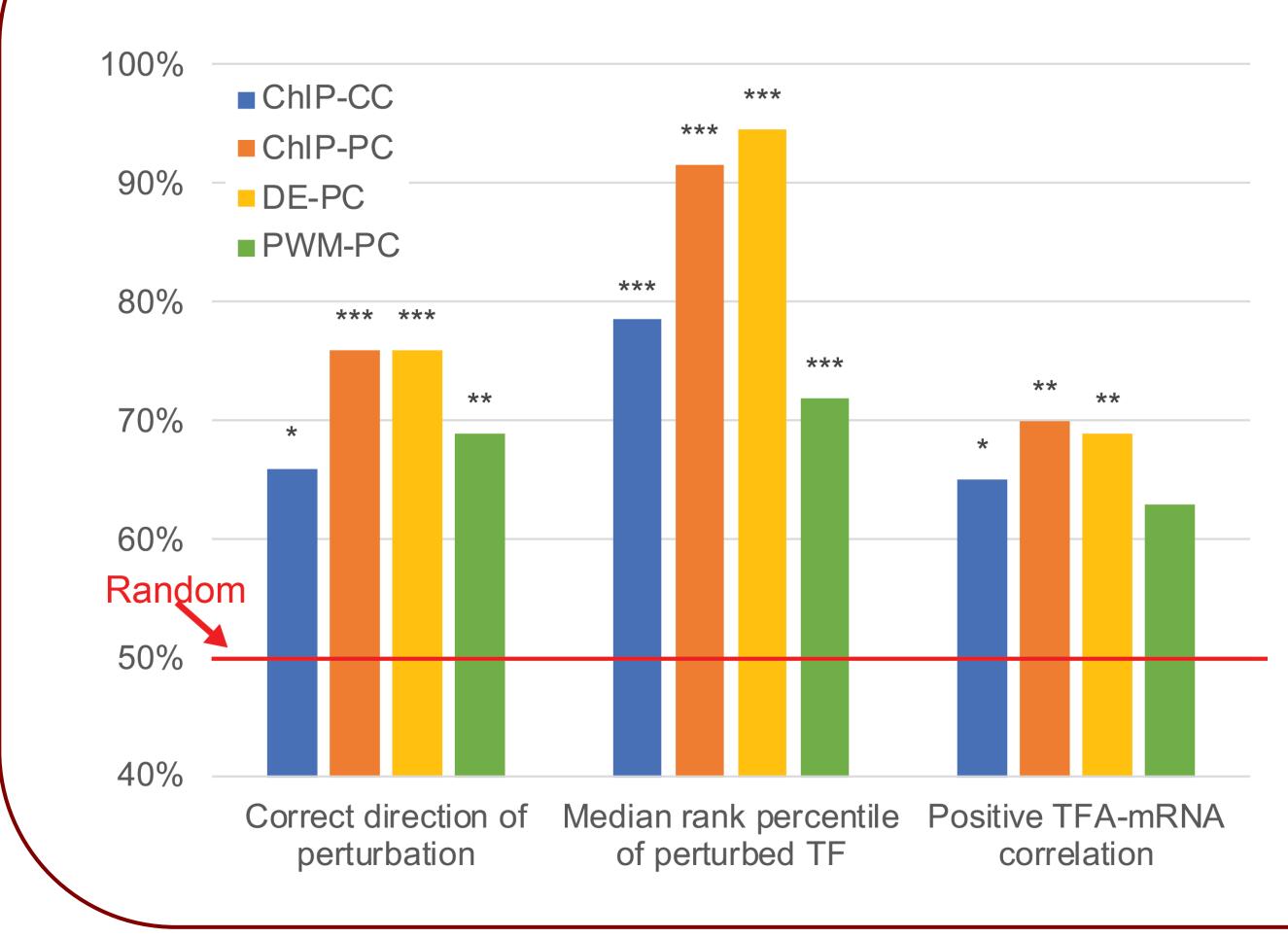
- 50 TF networks built with top ranked edges from ChIP, differential expression (DE) or log fold-change (LFC) after TF perturbation, or PWM
- TF-target edges defined repressing or activating using correlation of expression (CC) or expression after TF perturbation (PC)

Evaluation framework Samples Perturbation Constraint Samples generation Gene expression Samples Bilinear S X expression CS TFA Baselines Samples Linear model CS X expression expression Samples Correlation between TF ှတ့ TF expression activity and TF mRNA dataset 2 **Percent Positive** Samples φ Perturbation Perturbed TF prediction key 2 Perturbation Median Rank Direction

Performance metrics

- Correct direction of perturbation:
 - In samples where TFs are deleted/induced, percent correctly inferred activity values as less/greater than in the WT sample
- Median rank percentile of perturbed TF:
 In samples where TFs are deleted/induced, median rank of inferred activity levels compared to unperturbed TFs. Rank 1 = 100%
- Positive TFA-mRNA correlation:
 Percent of TFs whose inferred activity positively correlates with mRNA levels of their encoding genes

Performance of inferred TFA



Asterisks indicate significance of score:

* p < 0.01 ** p < 0.001 *** p < 0.0001

Impact of optimizing a quantitative network

