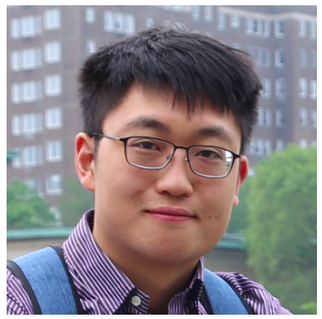
Active multiple testing w/ proxy p-value and e-values

DeGroot Workshop @ CMU 2025

Joint work with:



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Kathryn Roeder

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Carnegie Mellon University

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Goal: Use proxy statistics to derive
1. valid statistics for every hypothesis (correctness)
2. while selectively computing few true statistics (efficiency)

Outline

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    1.1. Active p-values
2. Application: scCRISPR screening via proximal causal inference
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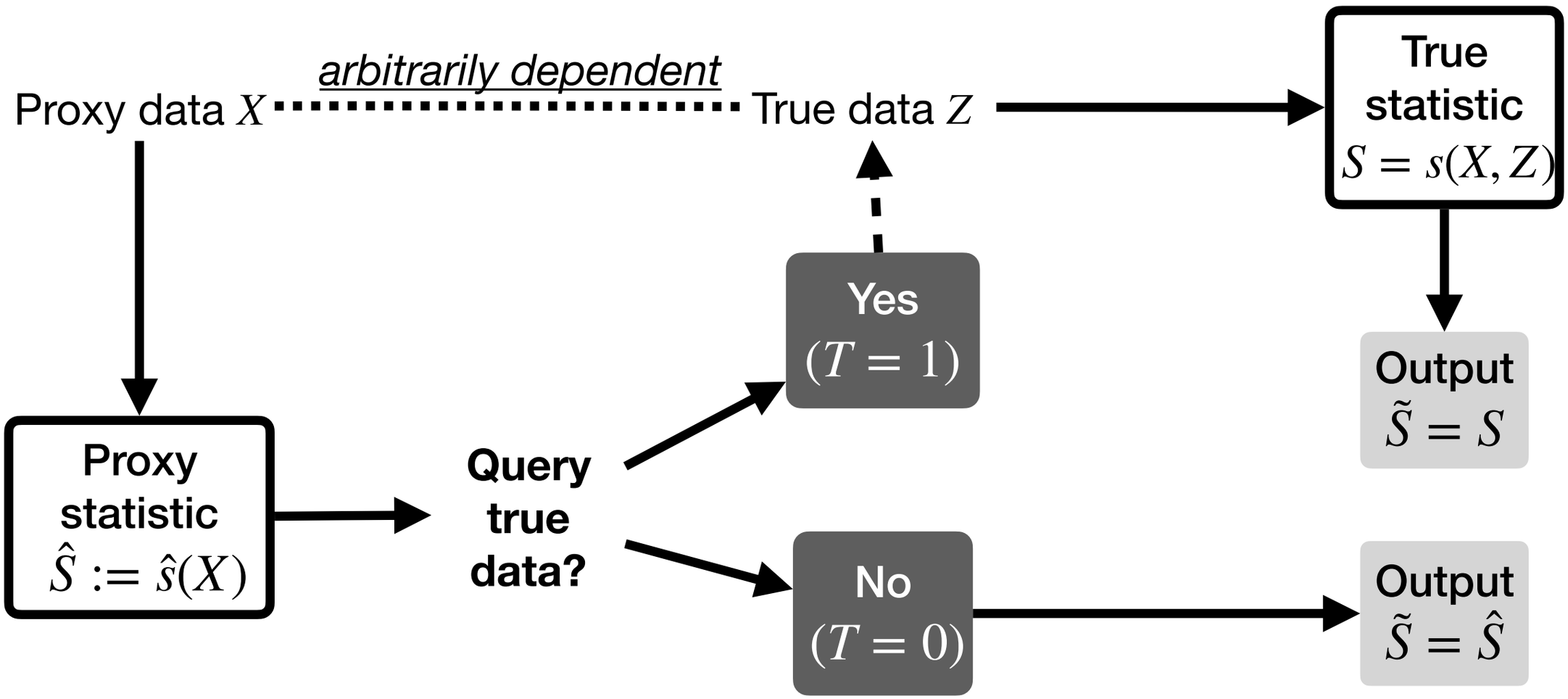
Active hypothesis testing framework



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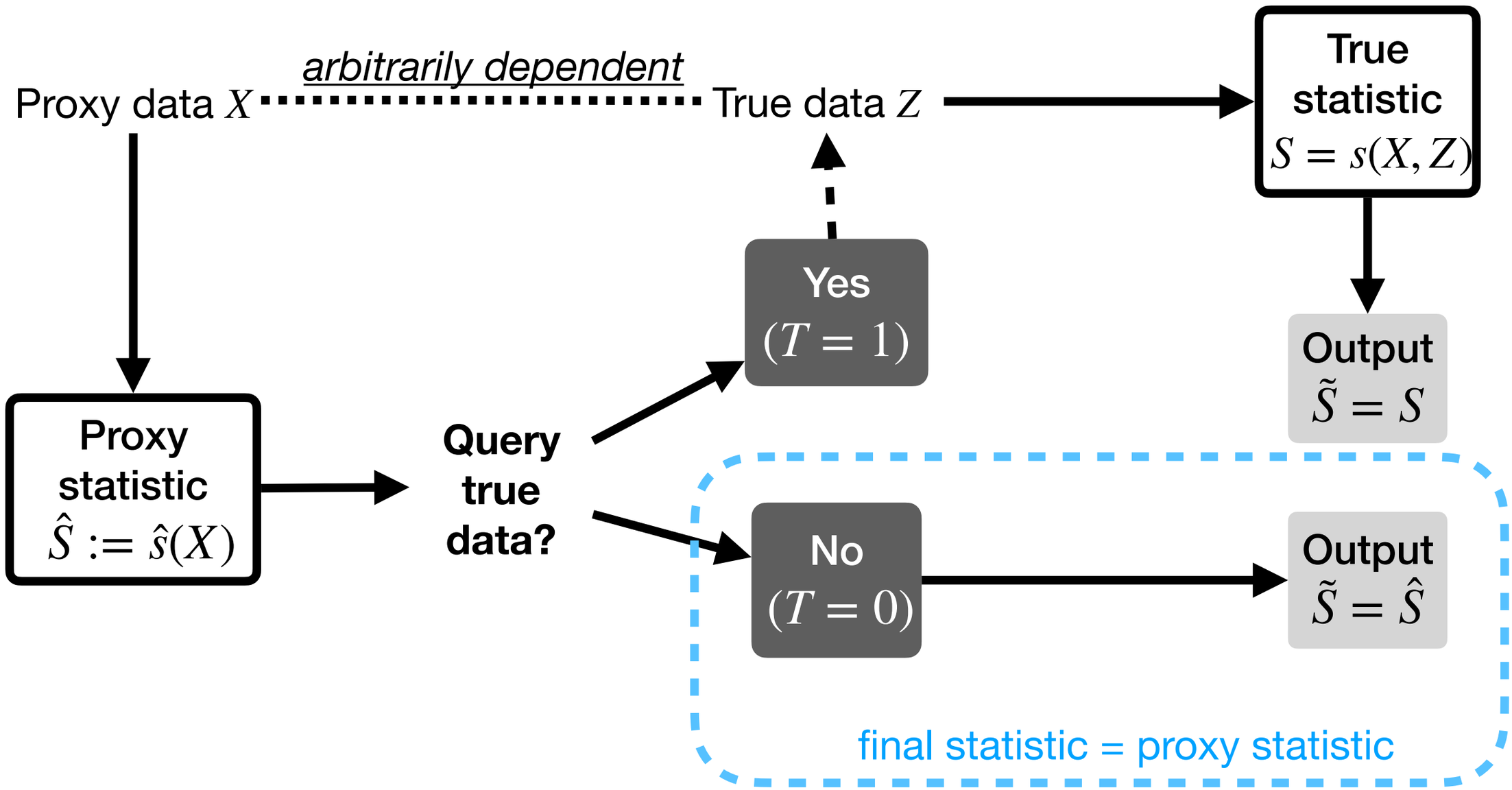

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Theorem (ours): Active p-values $\tilde{P}^{\text{arb-dep}}$ and $\tilde{P}^{\text{ind}}$ are bona-fide p-values.

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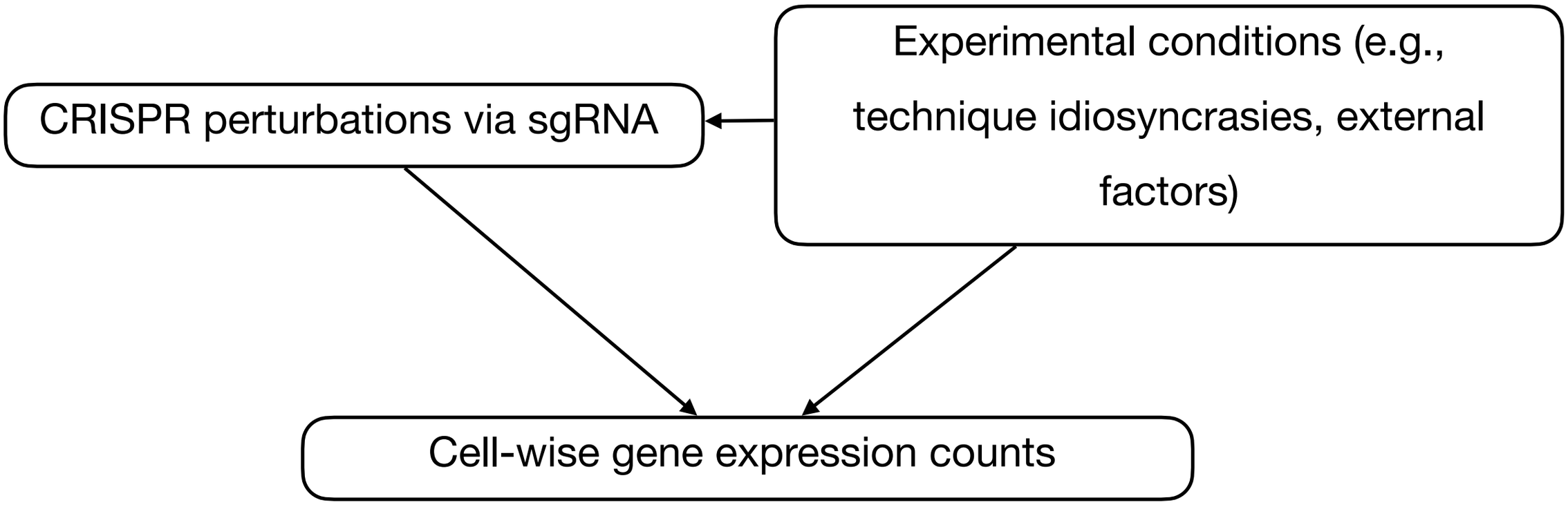
scCRISPR w/ gene perturbations



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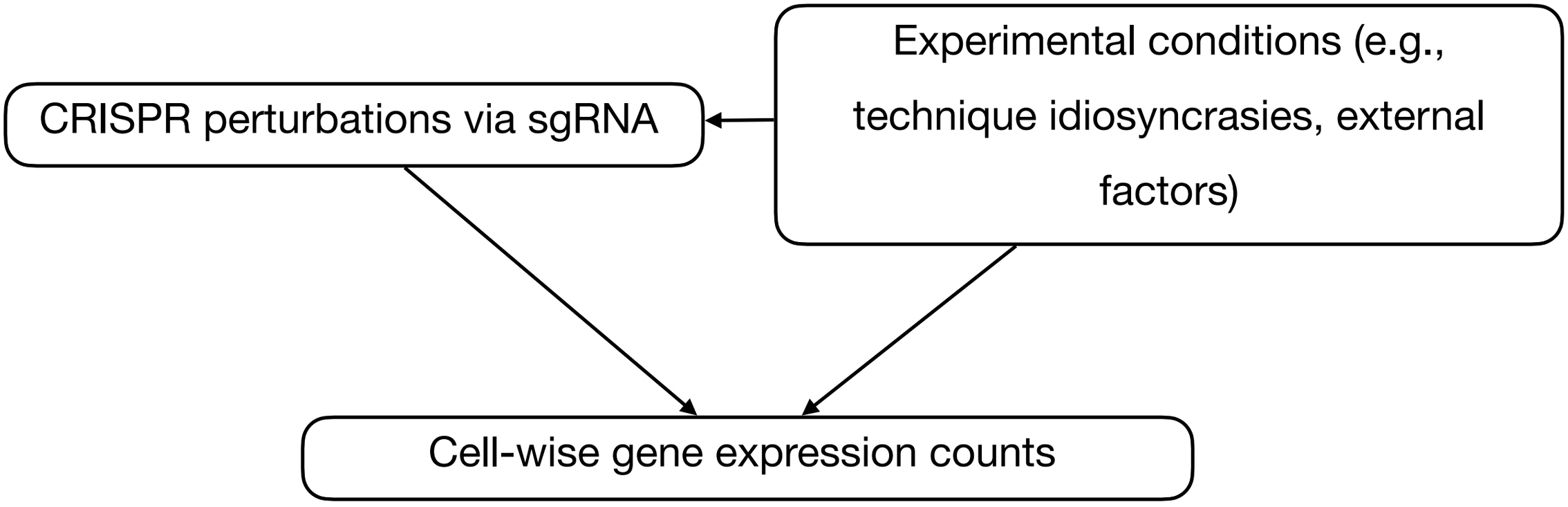

Goal: Test for causal effect of gene perturbation on cell-wise expression counts.

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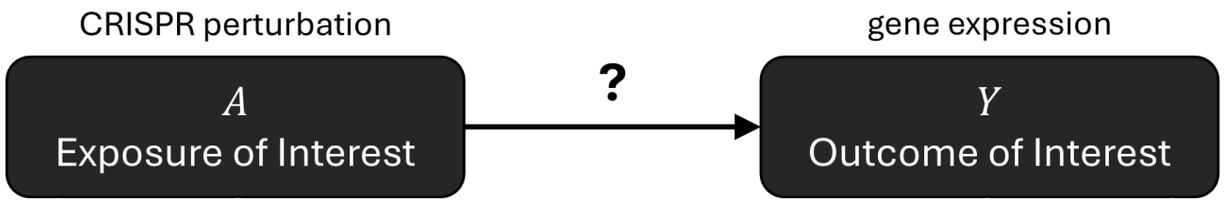

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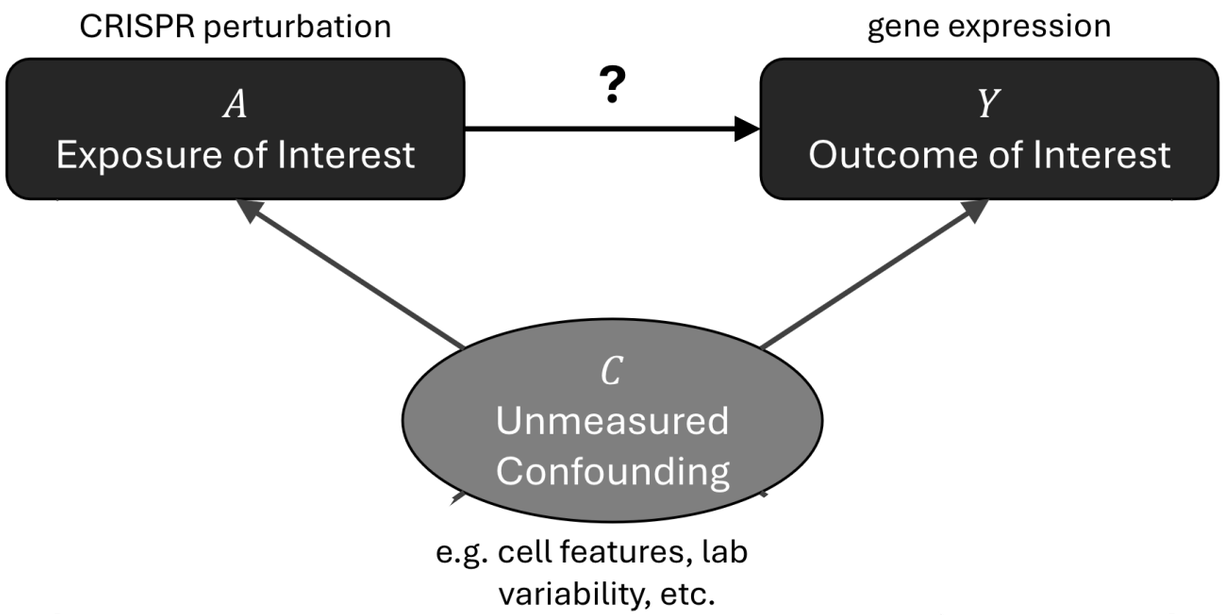

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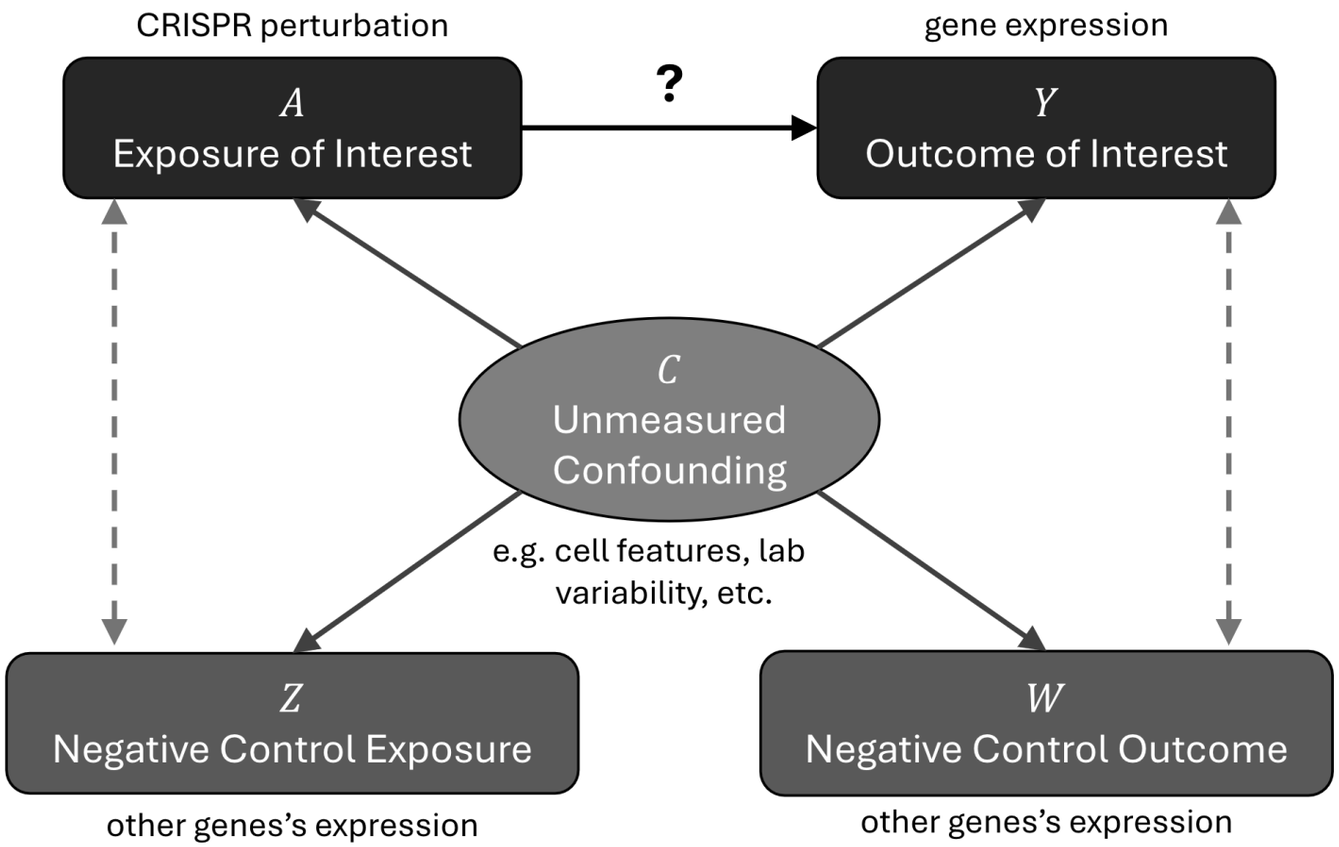

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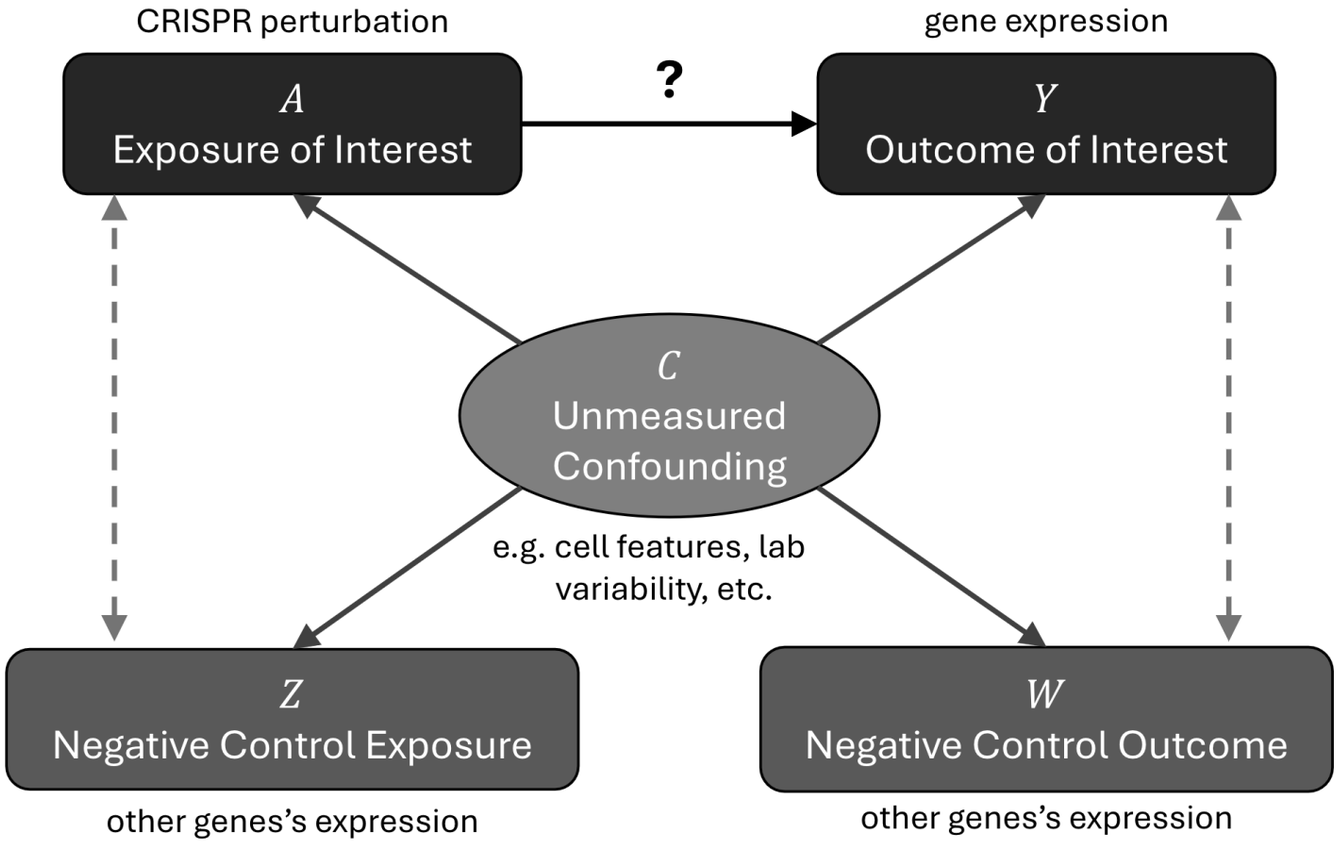

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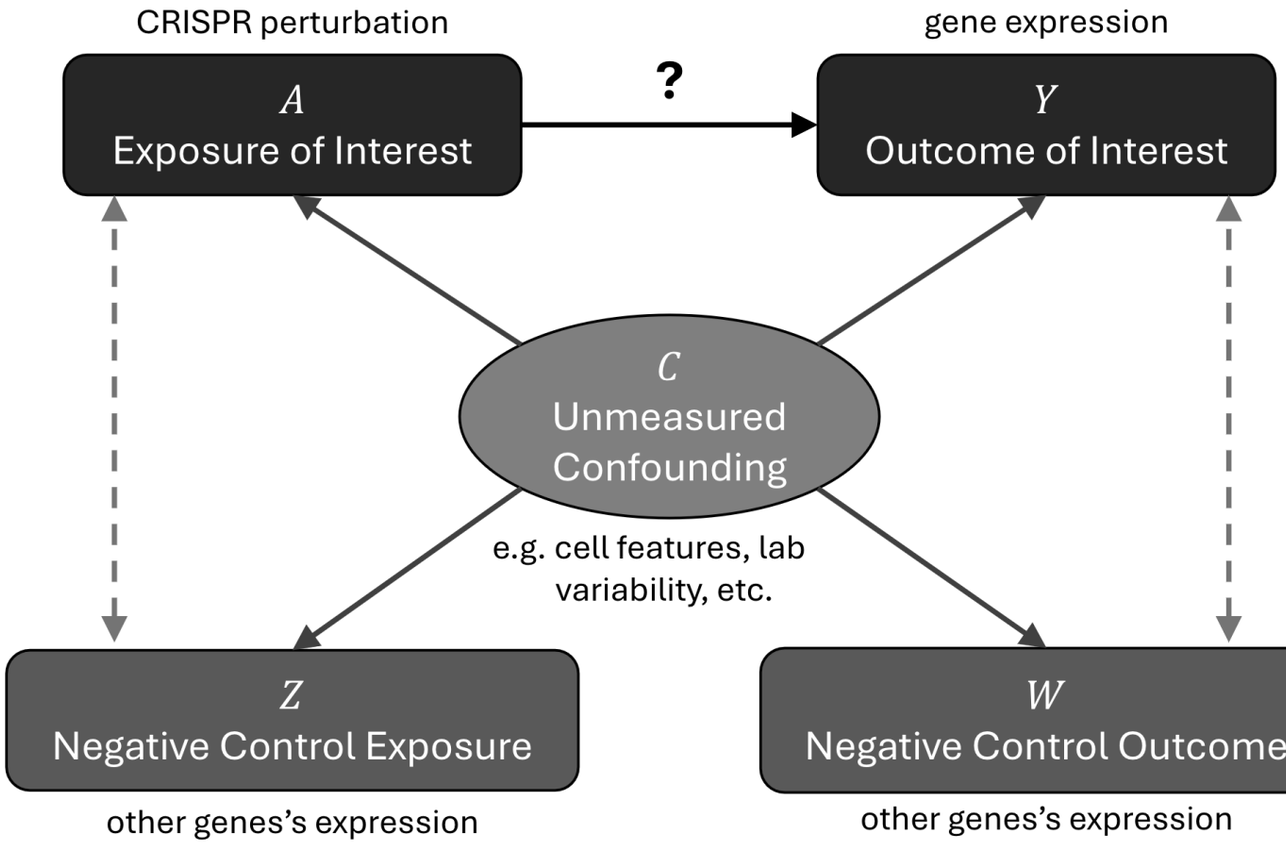

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this implies…

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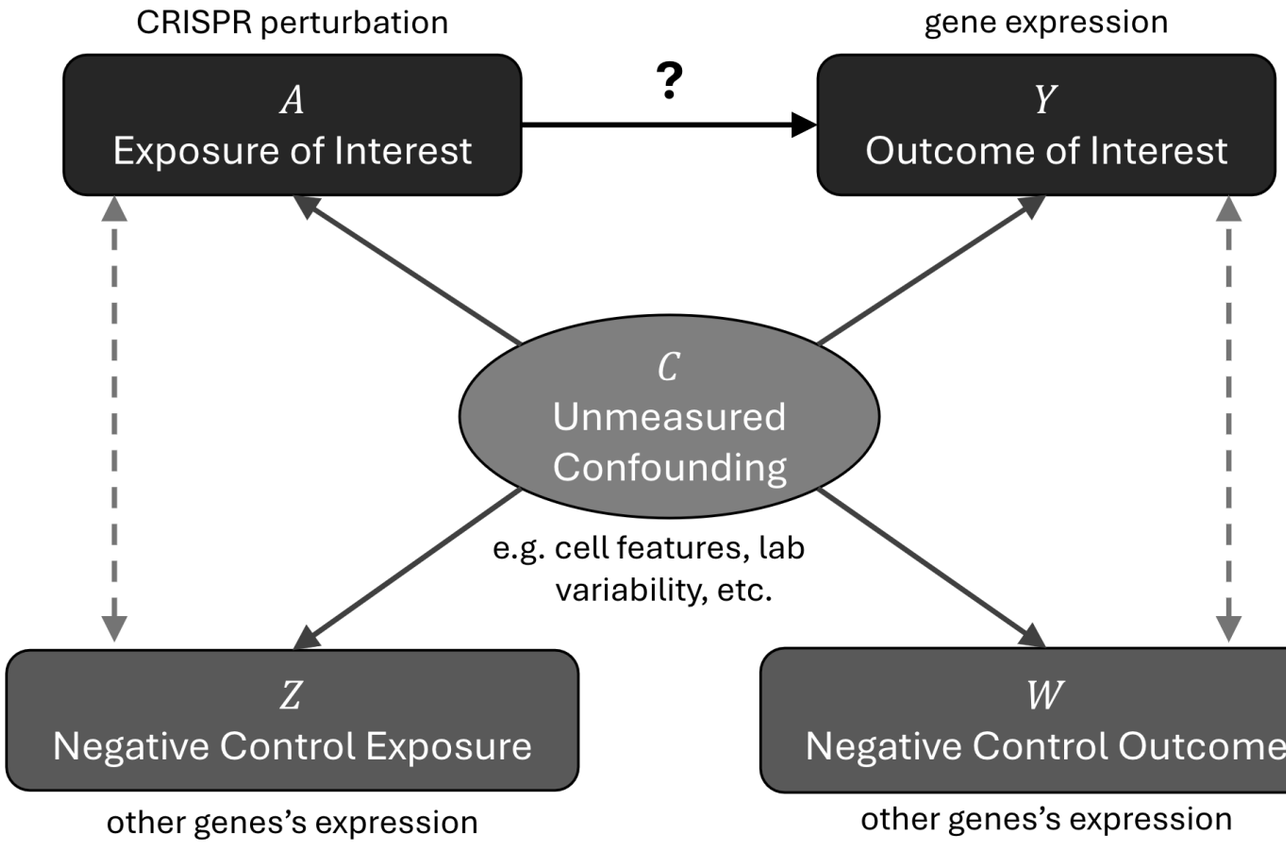

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We can run two stage-least squares to approximate $\mathbb{E}[W \mid A, Z]$ and estimate ψ^{ATE}.

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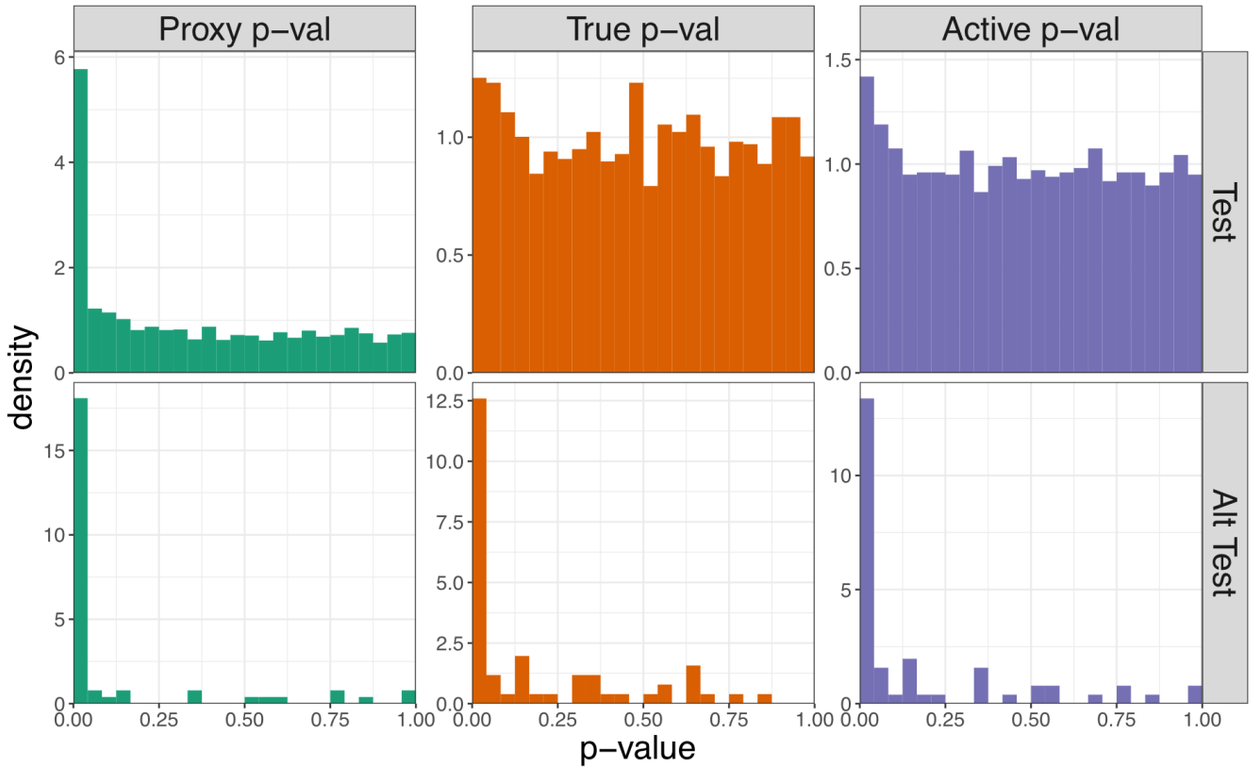
$O(nd^4)$ to compute $\hat{A}^{-1}$ and B.

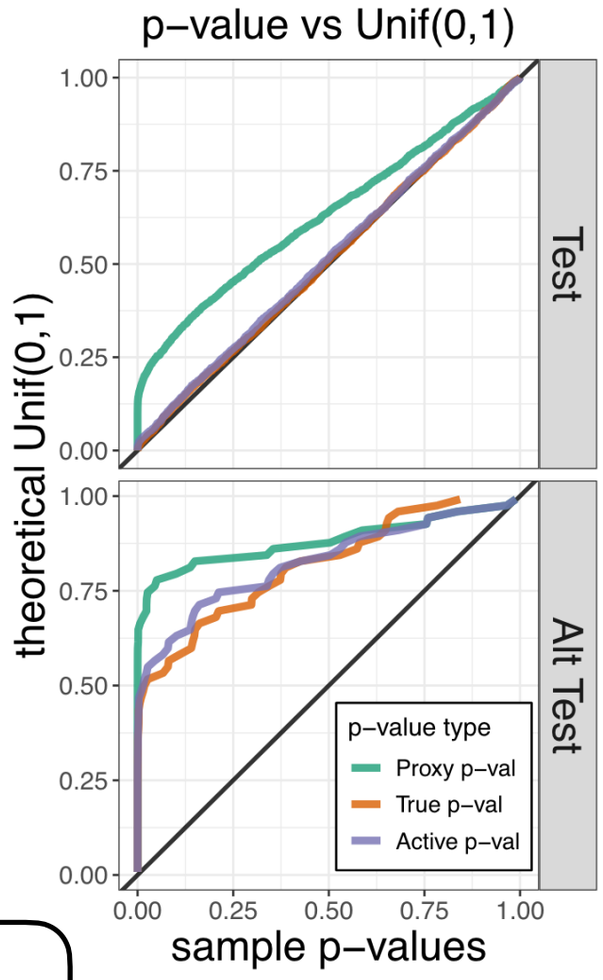
$O(d^6)$ to compute $\hat{A}^{-1} \hat{B} (\hat{A}^{-1})^T$.

Total complexity:

$O(nd^4 + d^6)$

Experimental results on scCRIPSR data

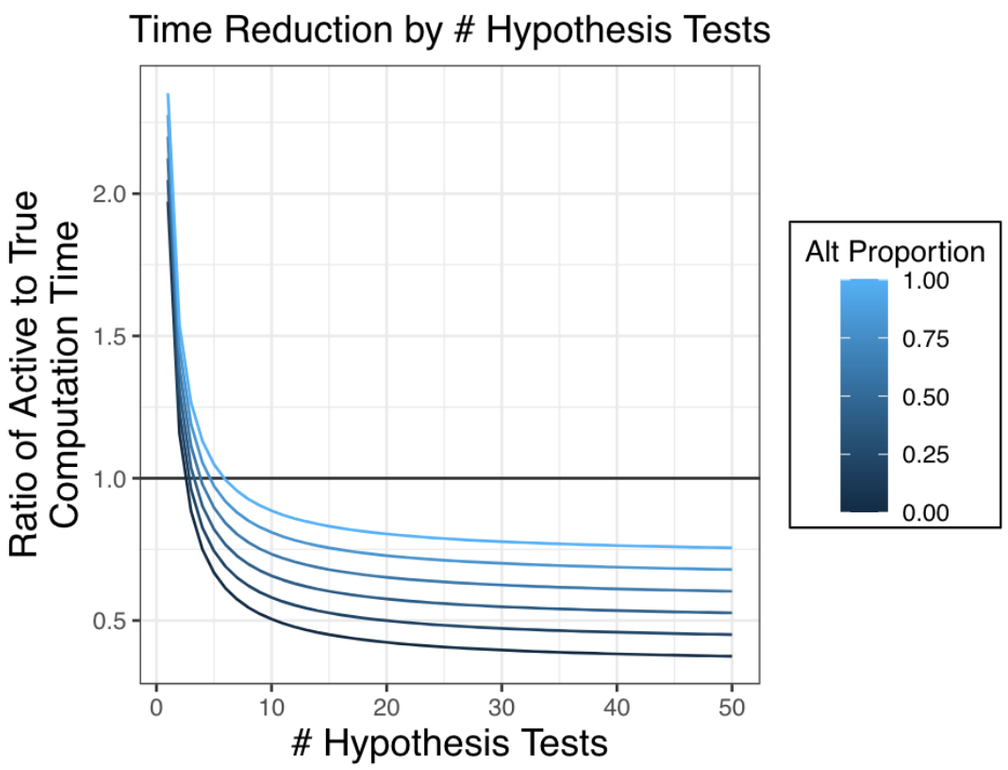


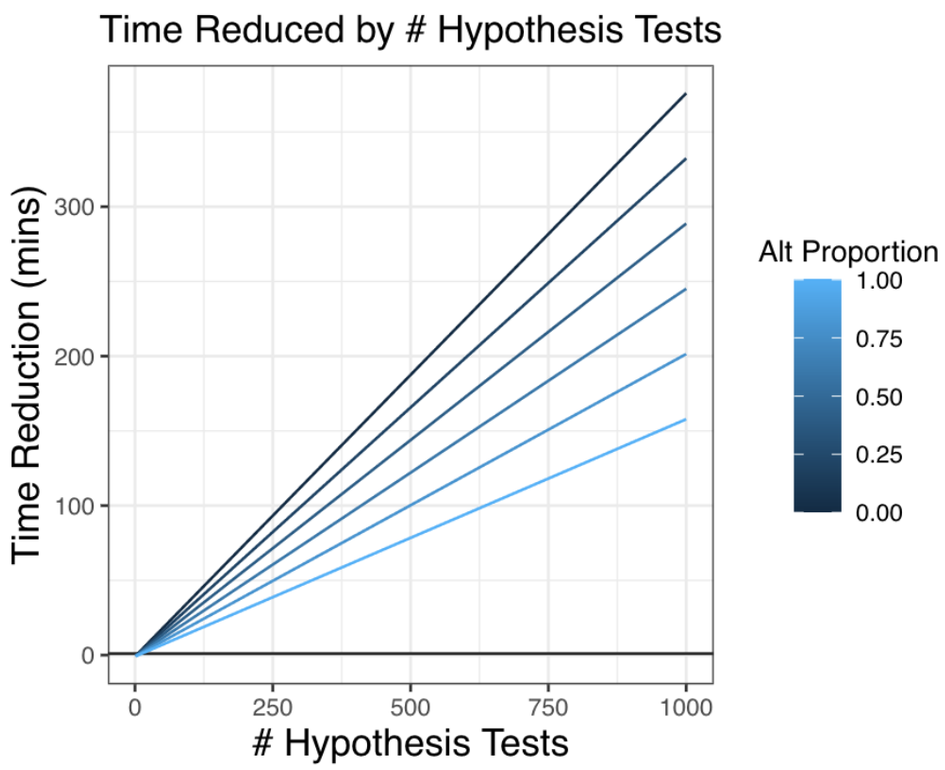


2000 genes pre-filtered [1] from original cancer marker scCRISPR dataset [2]. multimodal single-cell screens.

[1] Papalexi et al. Characterizing the molecular regulation of inhibitory immune checkpoints with
multimodal single-cell screens. *Nature Genetics,* 2021.
[2] Townes et al. Feature selection and dimension reduction for single-cell RNA-Seq based on a multinomial model *Genome Biology,* 2-10.

Experimental results on computation time





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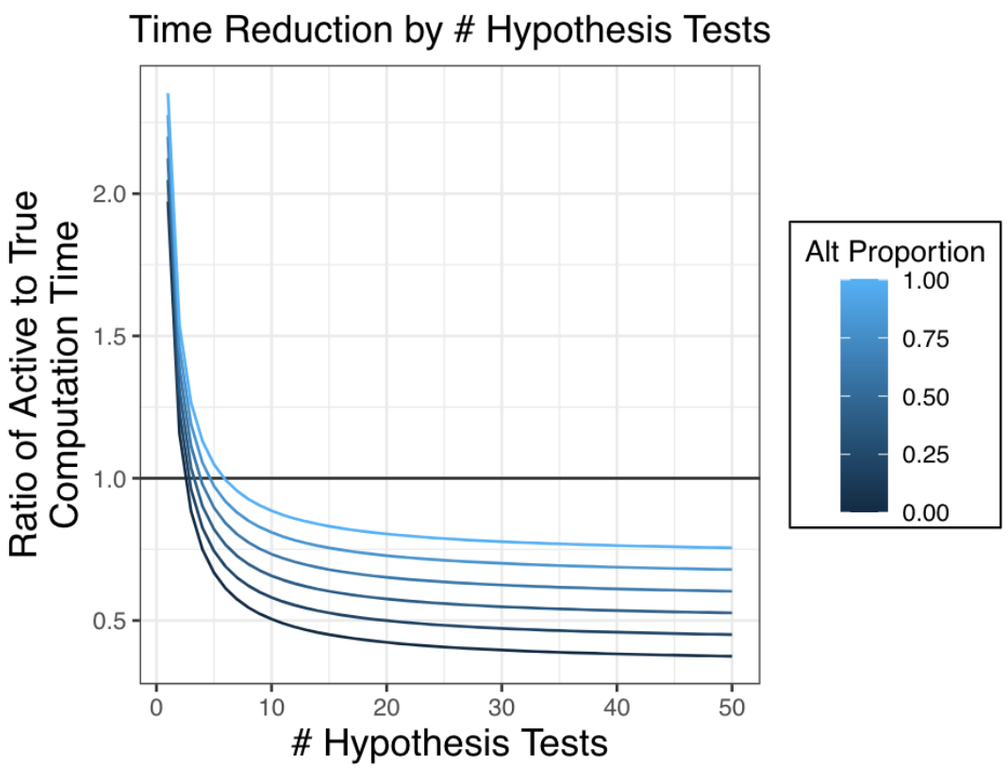

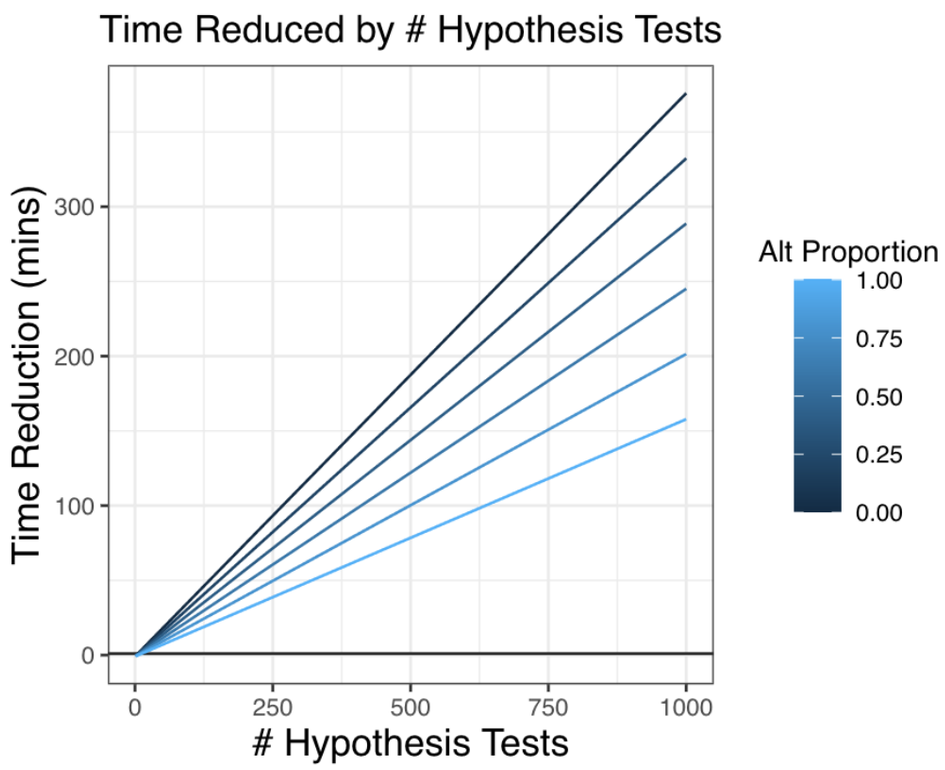

Significant reduction in computation time, while maintaining power.

Active BH for FDR control

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Multiple testing for K hypotheses —- $I_0 \subseteq [K]$ are the true nulls. Output discovery set $R \subseteq [K]$ s.t. *false discovery rate (FDR)*

$$\text{FDR} = \mathbb{E}\left[\frac{|I_0 \cap R|}{|R| \vee 1}\right] \leq \alpha \text{ for fixed } \alpha \in [0,1]$$

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Active BH procedure:

Access to $(Q_1, \ldots, Q_K)$ proxy p-values, and $(P_1, \ldots, P_K)$ are independent true p-values.

Apply Benjamini-Hochberg (BH) procedure to $(\tilde{P}_1, \ldots, \tilde{P}_K)$ (any active p-values), i.e.,

$$k^* = \max\left\{ k \in [K] : \sum_{i=1}^{K} \mathbf{1}\{\tilde{P}_i \leq \alpha k/K\} \geq k \right\} \text{ and } R = \{k \in [K] : P_k \leq \alpha k^*/K\}$$

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Theorem (ours): If $(P_1, \ldots, P_K)$ are independent, $(Q_1, \ldots, Q_K)$ are arbitrarily dependent, and (P_i, Q_i) satisfies active p-value dependence requirement, then FDR $\leq \alpha(1 + \log(1/\alpha))$.

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Thanks!

“Active multiple testing with proxy p-values and e-values”
arXiv:2502.05715