Robust differential expression testing for single-cell CRISPR screens

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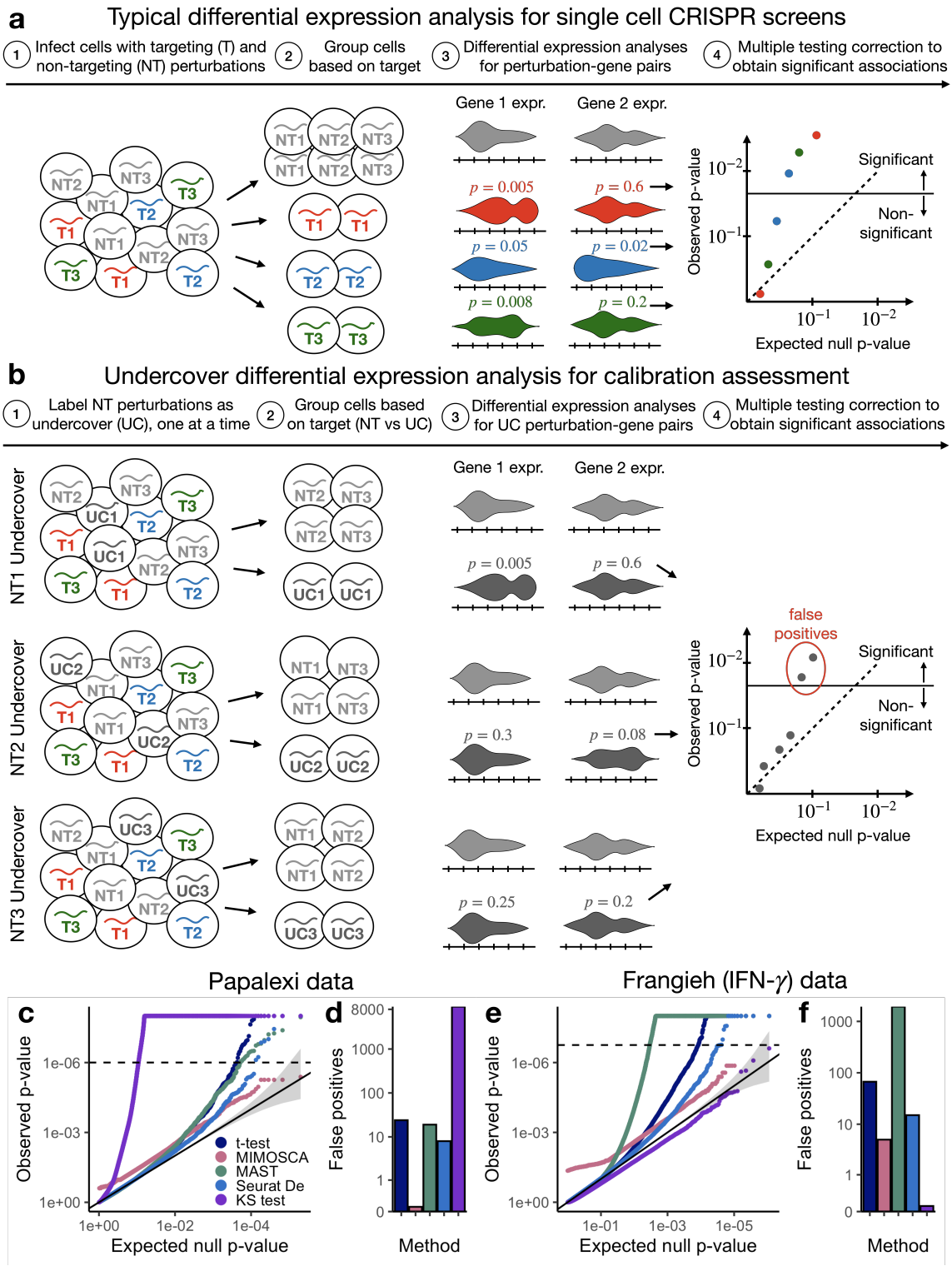
a
Typical differential expression analysis for single cell CRISPR screens
1 Infect cells with targeting (T) and non-targeting (NT) perturbations
2 Group cells based on target
3 Differential expression analyses for perturbation-gene pairs
4 Multiple testing correction to obtain significant associations
Gene 1 expr.
Gene 2 expr.
p = 0.005
p = 0.6
p = 0.05
p = 0.02
p = 0.008
p = 0.2
Observed p-value
Expected null p-value
Significant
Non-significant
b
Undercover differential expression analysis for calibration assessment
1 Label NT perturbations as undercover (UC), one at a time
2 Group cells based on target (NT vs UC)
3 Differential expression analyses for UC perturbation-gene pairs
4 Multiple testing correction to obtain significant associations
NT1 Undercover
NT2 Undercover
NT3 Undercover
p = 0.3
p = 0.08
p = 0.25
p = 0.2
false positives
Papalexi data
Frangieh (IFN-γ) data
c
d
e
f
Observed p-value
Expected null p-value
False positives
Method
t-test
MIMOSCA
MAST
Seurat De
KS test

Figure 1: Insert caption here.