(A) Consistency: 10X gene subset A vs. gene subset B GSE130931 GSE150068 GSE158941 GSE163505 $\begin{array}{c} \log(y/s+1) - \\ \operatorname{acosh}(2\alpha y/s+1) - \\ \log(y/s+1/(4\alpha)) - \\ \log(\operatorname{CPM}+1) - \\ \log(y/s+1) + \operatorname{HVG} - \\ \log(y/s+1) \to \operatorname{HVG} - \\ \log(y/s+1) \to \operatorname{HVG} \to \operatorname{Z} - \end{array}$ Delta Method Pearson sctransform Analytic Pearson Random Quantile Pearson (no clip) Pearson → HVG Pearson → Z Pearson → Z **GLM Residuals** Expr. Sanity MAP Sanity Distance Dino Normalisr Ę. GSE164017 GSE178765 GSE17971 GSE179831 GSE184806 $\begin{array}{c} \log(y/s+1) \\ \operatorname{acosh}(2\alpha y/s+1) \\ \log(y/s+1/(4\alpha)) \\ \log(\operatorname{CPM}+1) \\ \log(y/s+1) \rightarrow \operatorname{HVG} \\ \log(y/s+1) \rightarrow \operatorname{HVG} \\ \log(y/s+1) \rightarrow \operatorname{TVG} \rightarrow \operatorname{Z} \end{array}$ Delta Method Pearson sctransform Analytic Pearson Random Quantile **GLM Residuals** Pearson (no clip) Pearson→HVG Pearson→Z Pearson→HVG→Z Exp. Sanity MAP Sanity Distance Dino Normalisr Ľ Count GLM PCA NewWave 300 10 10 k-NN Overlap (B) Simulation: Ground truth vs. simulated counts Linear Walk Random Walk scDesign2 Dyngen muscat Delta Method Pearson sctransform Analytic Pearson Random Quantile Pearson (no clip) Pearson→HVG Pearson→Z Pearson→HVG→Z **GLM Residuals** Sanity MAP Sanity Distance Dino Normalisr Exp. Lat. Count GLM PCA NewWave k-NN Overlap (C) Downsampling: Original vs. downsampled Smart-seq3 data mcSCRB Fibroblasts (ss3) HEK (ss3) siRNA KD (ss3) Fibroblasts 2 (ss3) $\begin{array}{c} \log(y/s+1) \\ \operatorname{acosh}(2\alpha y/s+1) \\ \log(y/s+1/(4\alpha)) \\ \log(\operatorname{CPM}+1) \\ \log(y/s+1) \rightarrow \operatorname{Iog}(y/s+1) \rightarrow \operatorname{Iog}(y/s+1)$ Delta Method Residuals

Pearson sctransform Analytic Pearson Random Quantile Pearson (no clip) Pearson→HVG Pearson→Z Pearson→HVG→Z GLM Expr. Sanity MAP Sanity Distance Dino Normalisr Ę. GLM PCA NewWave k-NN Overlap