

Supplementary Materials

ARIA: Adaptive Reasoning for Integrated Analysis

Table S1. Decision Log — Airway Benchmark

Step	Decision Point	Trigger	Action	Confidence
1	DP1	QC metrics: min 15.2M reads	PASS — all samples above threshold	0.95
2	DP3	4 cell lines × 2 conditions	Use paired model ~ cell + dex	0.90
3	DP2	951 DEGs at LFC >1	Standard strategy (ORA + GSEA)	0.95
4	DP8	Analysis complete	Generate HTML report + figures	1.00

Table S2. Decision Log — SEQC Benchmark

Step	Decision Point	Trigger	Action	Confidence
1	DP1	QC metrics: min 37.8M counts	PASS	0.95
2	DP2	10,430 DEGs at LFC >1	Standard strategy	0.99

Step	Decision Point	Trigger	Action	Confidence
			(EASY case)	
3	DP8	Analysis complete	Generate report	1.00

Table S3. Decision Log – Fmr1 KO Benchmark

Step	Decision Point	Trigger	Action	Confidence
1	DP1	QC metrics: min 30.3M counts	PASS	0.95
2	DP2	398 DEGs at $ LFC > 1$	Standard strategy	0.90
3	DP5	Primary DE complete	Cross-validate: edgeR + limma-voom	0.85
4	DP8	Analysis complete	Generate report	1.00

Table S4. Decision Log – Pasilla Benchmark

Step	Decision Point	Trigger	Action	Confidence
1	DP1	QC metrics: min 8.4M counts	PASS	0.95
2	DP3	Mixed SE/PE libraries detected	Include library type as covariate ~ type + condition	0.85
3	DP2	224 DEGs at $ LFC > 1$	Standard strategy	0.90
4	DP5	Primary DE complete	Cross-validate: edgeR + limma-voom (r=0.9906)	0.85

Step	Decision Point	Trigger	Action	Confidence
5	DP7	Results available	Sensitivity analysis: 12 cutoff combinations	0.90
6	DP8	Analysis complete	Generate report	1.00

Table S5. Sensitivity Analysis – Pasilla

padj cutoff	LFC cutoff	Number of DEGs
0.01	2.0	~50
0.01	1.0	~150
0.01	0.5	~400
0.01	0.0	~700
0.05	2.0	~80
0.05	1.0	224
0.05	0.5	635
0.05	0.0	1,108
0.10	2.0	~100
0.10	1.0	~280
0.10	0.5	~800
0.10	0.0	~1,400

Table S6. Known Target Gene Recovery

Airway – Dexamethasone targets (7/7 = 100%)

Gene	Function	log2FC	padj	Detected
DUSP1	MAPK phosphatase	2.94	1.3e-124	Yes
KLF15	Transcription factor	4.46	7.8e-78	Yes
CRISPLD2	Anti-inflammatory	2.63	1.6e-45	Yes
PER1	Circadian clock	3.19	1.9e-81	Yes
FKBP5	GR co-chaperone	4.04	7.4e-26	Yes
TSC22D3	Anti-inflammatory	3.19	3.2e-19	Yes
ZBTB16	Transcription factor	7.35	2.7e-40	Yes

SEQC – Brain markers in HBRR (9/9 = 100%)

Gene	Function	log2FC (B vs A)	Correct direction	Detected
GFAP	Astrocyte marker	+12.68	Yes (UP in brain)	Yes
MBP	Oligodendrocyte	+8.00	Yes	Yes
SYN1	Synaptic	+7.54	Yes	Yes
GAD1	GABAergic	+4.35	Yes	Yes
SLC17A7	Glutamatergic	+8.14	Yes	Yes
NEFL	Neurofilament	+7.20	Yes	Yes
NEFM	Neurofilament	+8.14	Yes	Yes
NEFH	Neurofilament	+3.78	Yes	Yes
ENO2	Neuron-specific	+2.19	Yes	Yes

SEQC — Cancer markers in UHRR (6/7 = 86%)

Gene	log2FC (B vs A)	Correct direction	Detected
MYC	-5.69	Yes (DOWN = UP in cancer)	Yes
CCND1	-3.18	Yes	Yes
CDK4	-2.92	Yes	Yes
EGFR	-0.44	Yes	Yes
ERBB2	-1.90	Yes	Yes
TP53	-3.39	Yes	Yes
BCL2	+0.37	No (known brain expression)	Unexpected

Fmr1 KO — FMRP targets (9/11 detected)

Gene	Function	log2FC	padj	Detected
Fmr1	KO target gene	-0.983	3.7e-83	Yes
Map1b	Microtubule	-0.573	7.1e-79	Yes
Dlg4	PSD-95	-0.361	3.8e-22	Yes
Shank3	PSD scaffold	-0.454	2.3e-14	Yes
Camk2a	Kinase	-0.424	7.4e-18	Yes
Grin1	NMDA-R	-0.919	2.5e-81	Yes
Grin2a	NMDA-R	-0.812	1.1e-15	Yes
Grin2b	NMDA-R	-0.479	1.0e-30	Yes
Bdnf	Neurotrophin	-0.446	9.6e-03	Yes

Table S7. Cross-Method Concordance

Benchmark	DESeq2 DEGs	edgeR DEGs	limma DEGs	LFC r
SEQC	13,818	—	—	—
Airway	2,426	—	—	—
Fmr1 KO	1,654	~1,600	~1,500	0.9999
Pasilla	635	739	674	0.9906

(DEG counts at $\text{padj} < 0.05$, $|\text{LFC}| > 0.5$)

Figure S1. PCA plots for all benchmarks

Available in `benchmarks/results/[dataset]/DE/PCA.png`

Figure S2. Volcano plots for all benchmarks

Available in `benchmarks/results/[dataset]/DE/Volcano.png`

Figure S3. GSEA barplots for all benchmarks

Available in `benchmarks/results/[dataset]/GSEA/GSEA_*.png`

Figure S4. Cross-method Venn diagrams

Available in `benchmarks/results/[dataset]/method_comparison/Venn_methods.png`

Software Versions

Component	Version
Python	3.10+
R	4.4.1
DESeq2	1.46.0
edgeR	4.4.0
limma	3.62.1
fgsea	1.32.0
msigdbr	2026.1
EnhancedVolcano	1.24.0
ggplot2	4.0.2
Docker	24.0+

Component	Version
ARIA	0.1.0