Method writing:

(1) GSEA

1. For each cell type (49 cell types in total), we first obtain the number of genes with enrichment scores greater than a pre-specified threshold\*\* from the single cell enrichment score data.
2. According to the directionality of the effect/condition (here, effect/condition can be aging continuous, aging binary, MDD, etc.), we perform the following GSEA test separately for up-regulated and down-regulated genes (and also up+down).
3. Gene Set Enrichment Analysis (GSEA) test was performed using the significance level (-log10(AW-Fisher qvalue), -log10(raw pvalue), etc.) as the weight to see whether the effect-related significance of those enriched genes is different from that of the background genes. Significance of the test was obtained by permuting the gene labels for 1000 times and to increase the precision of the permutation test, we shared the information across the 49 different cell types.

(2) AUROC

1. All the tested genes were first sorted from highly significant up-regulated genes to highly significant down-regulated genes.
2. AUROC was computed for a specific cell type with the given list of enriched genes. Thus, AUROC < 0.5 would suggest genes specific to that cell type are down-regulated with the effect while AUROC > 0.5 indicated that the genes are up-regulated for a cell type.
3. The p-value for comparing the significance of enriched genes vs the background genes was obtained from the non-parametric Wilcoxon rank sum test.

\*\* Selection criteria: for Aging gene expression data, we used enrichment score >2; for all the rest, we used enrichment score > 1.5.

GSEA formula details:

