**Supplementary Materials**

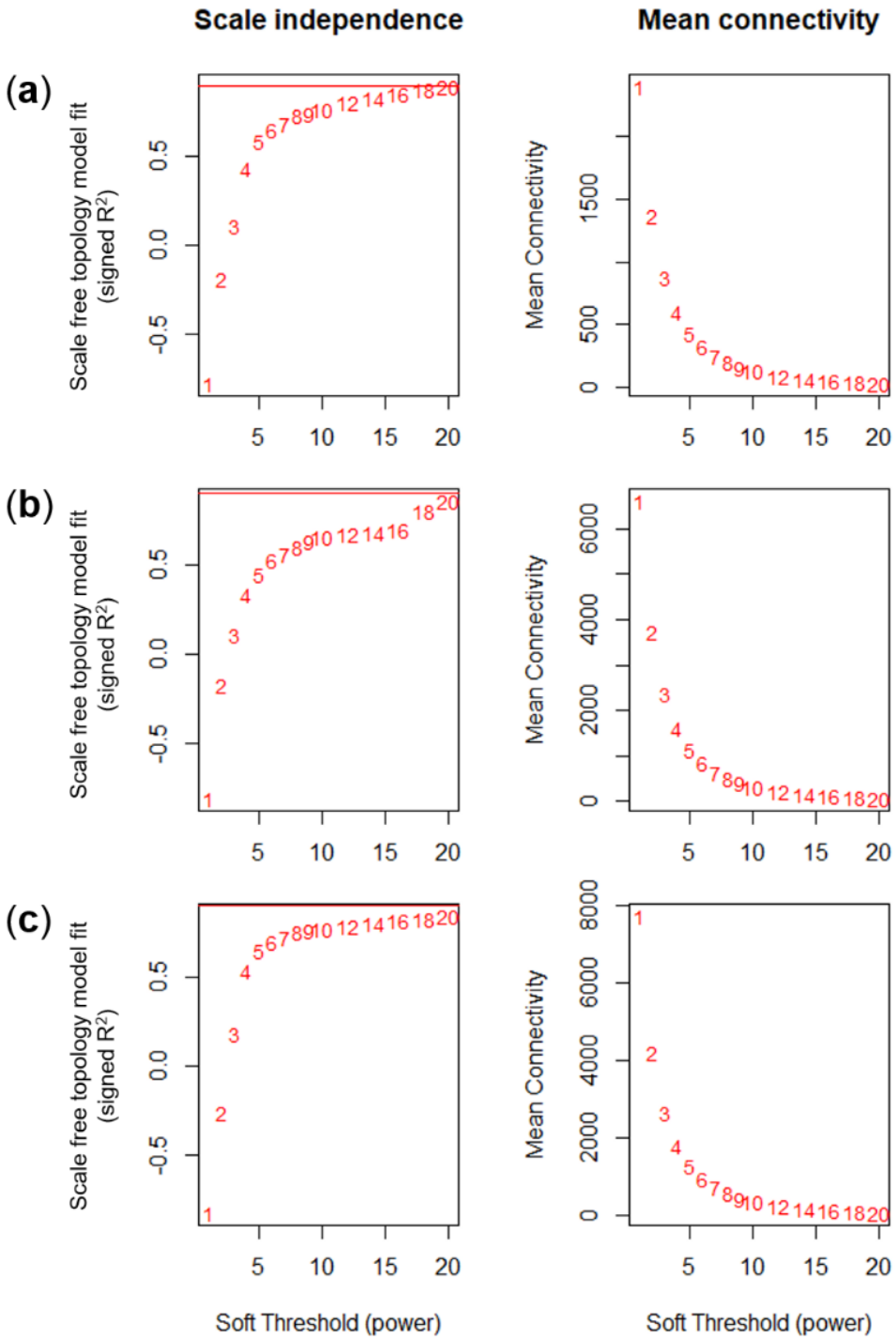


Figure S1. Scale-free topology fit using the WGCNA package for sample cohorts of (**a**) H1N1, (**b**) pH1N1 and (**c**) H5N1.

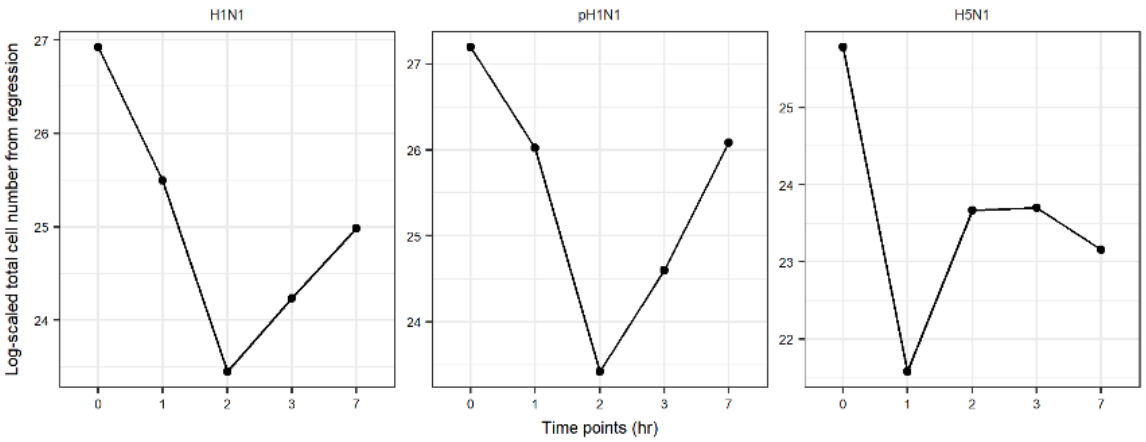


Figure S2. The estimated total number of cells in influenza virus-infected samples does not change significantly in the 7-day time course. Since the fraction of a cell type is equal to the number of this cell type divided by the total number of all cells in a sample, we have the following equation to connect total cell numbers with cell fractions: $\boldsymbol{c_t} \cdot x_t = \boldsymbol{f_t}$, where $\boldsymbol{c_t}$ is a vector of averaged cell fractions for n kinds of cells at time t predicted by CIBERSORT, $\boldsymbol{f_t}$ is a vector with the same length which represents averaged cell counts at time t measured by FACS, and the total number of cells at time t is represented as $x_t$. The values of $x_t$ at all time points are estimated using linear regression (by the R function "lm"). We observe that these $x_t$ values are relatively unvaried referring to the much smaller numbers of immune cells (Figure 2 & Figure S1).

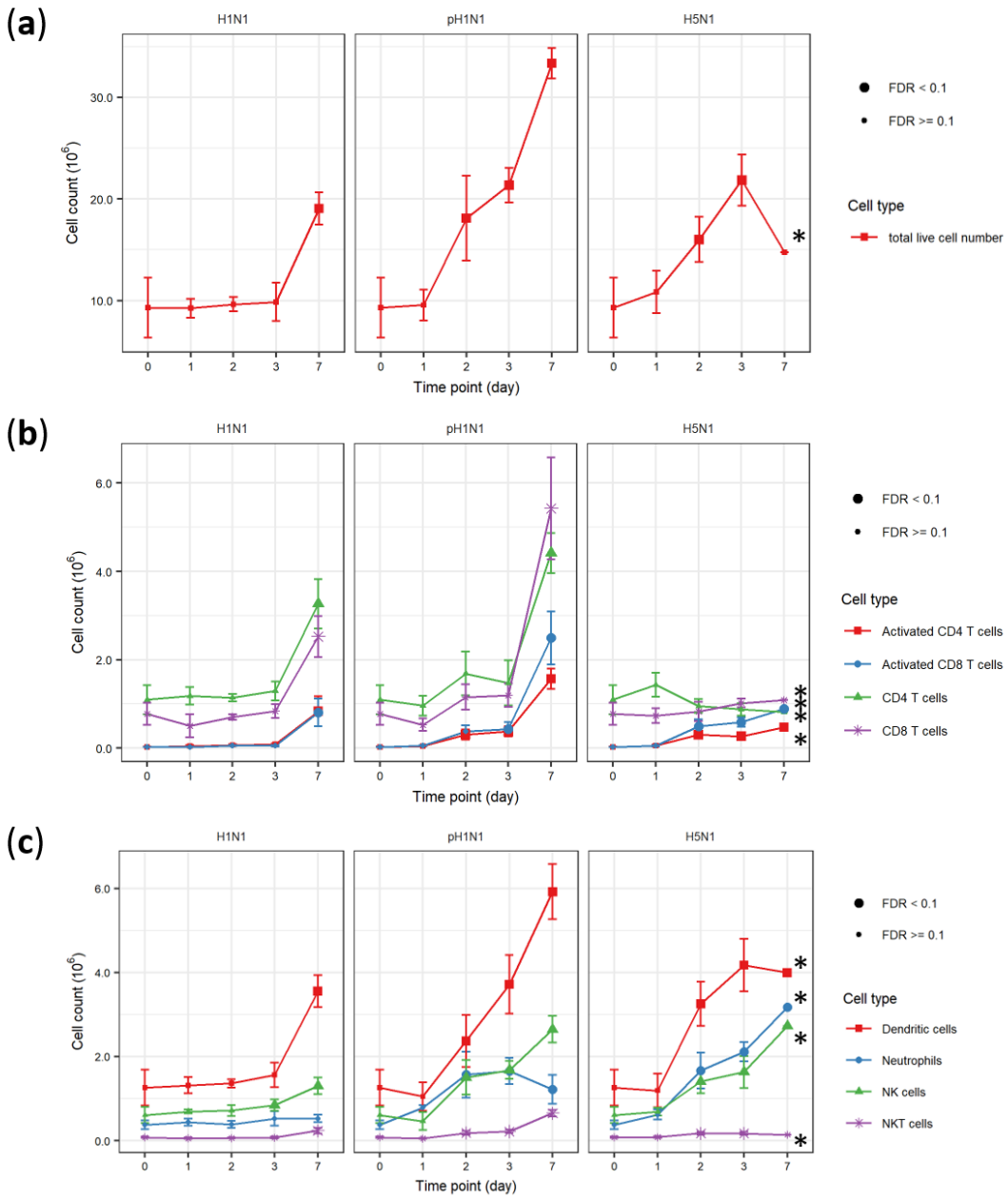


Figure S3. Cell counts of (**a**) total live cells, (**b**) T cell subsets, (**c**) neutrophils, DCs, NK cells and NKT cells in mouse lungs after infection by either H1N1, pH1N1 or H5N1 virus. Day 0 data are from uninfected, control animals. *Animals infected by H5N1 died before Day 7.

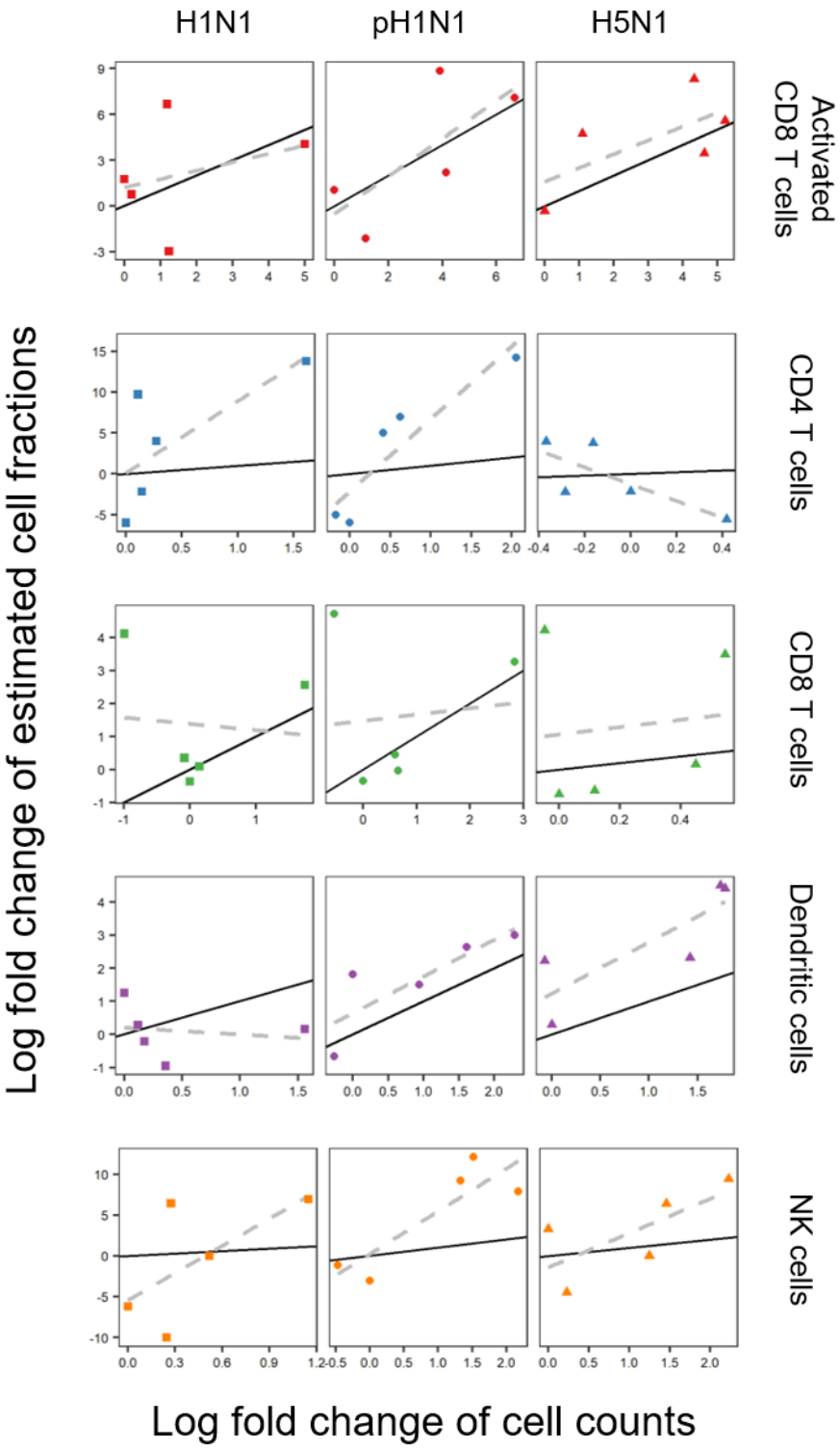


Figure S4. Log fold change of estimated cell fractions by CIBERSORT in comparison with log fold change of cell counts measured by FACS for different cell types. The black line is y = x while the grey dashed line is regression.

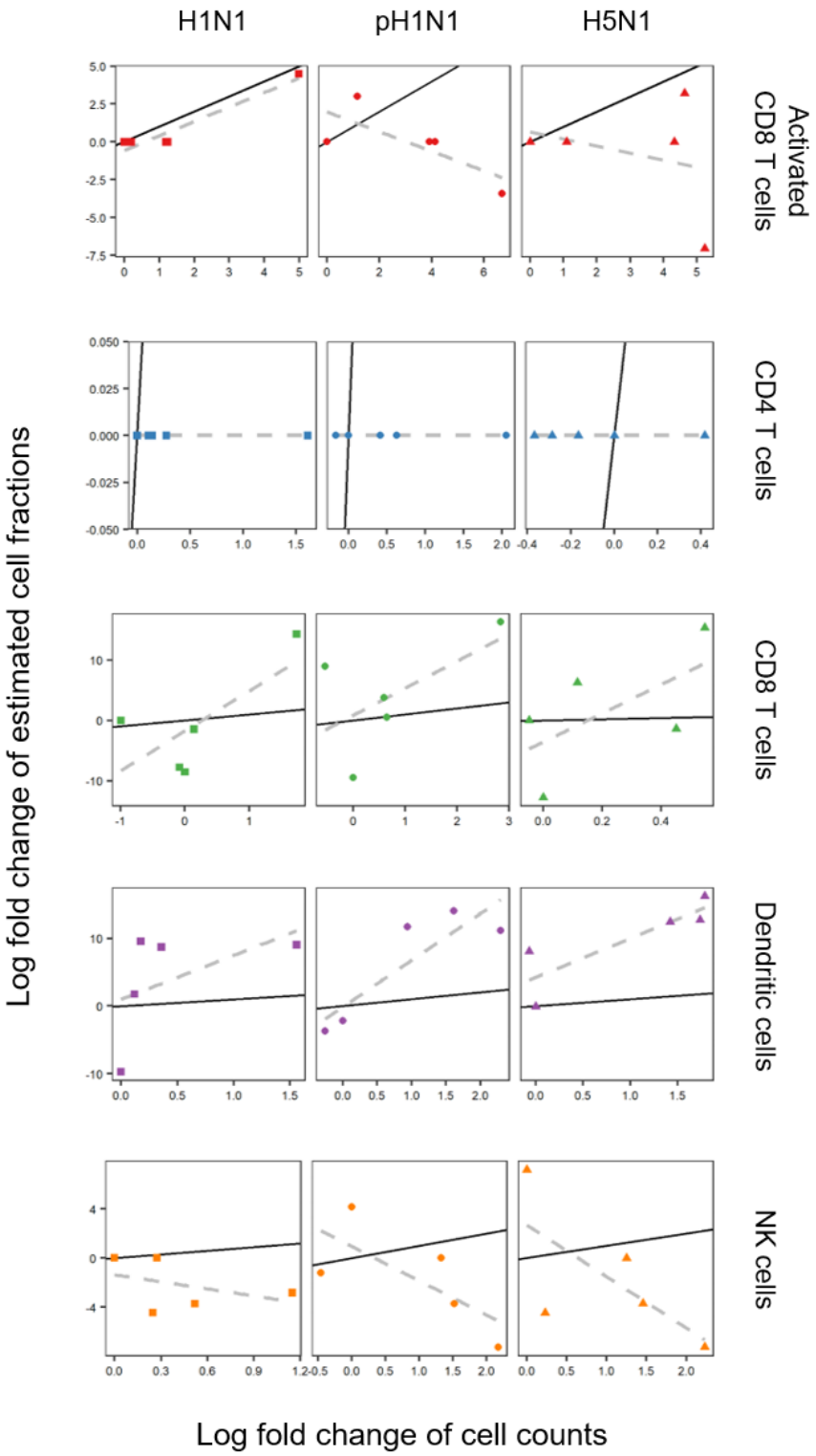


Figure S5. Log fold change of estimated cell fractions by MLLSR in comparison with log fold change of cell counts measured by FACS for different cell types. The black line is y = x while the grey dashed line is regression.

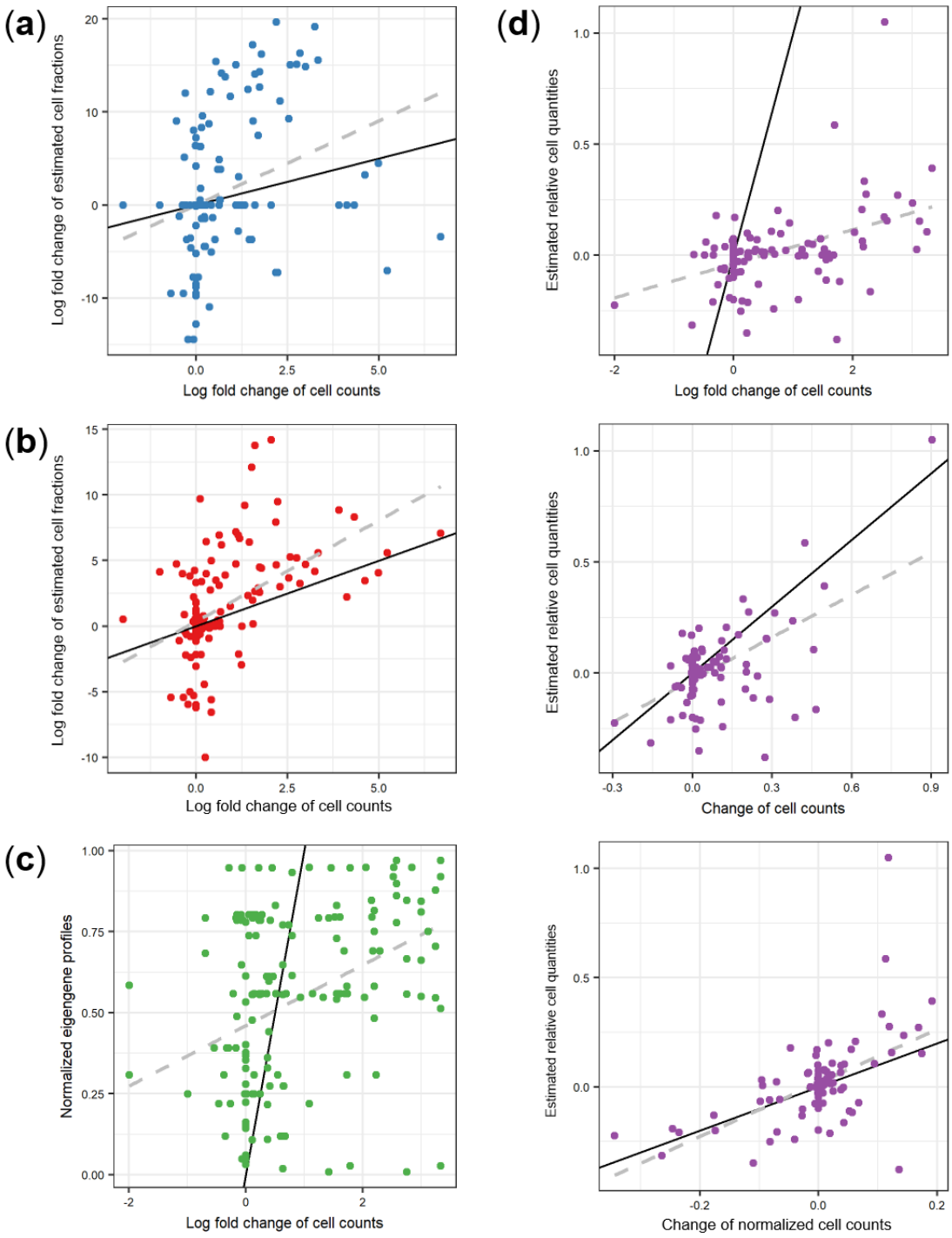


Figure S6. Estimated cell quantities by (**a**) MLLSR, (**b**) CIBERSORT, (**c**) CTen, and (**d**) DCQ in comparison with normalized cell counts measured by FACS. The black line is y = x while the grey dashed line is regression.

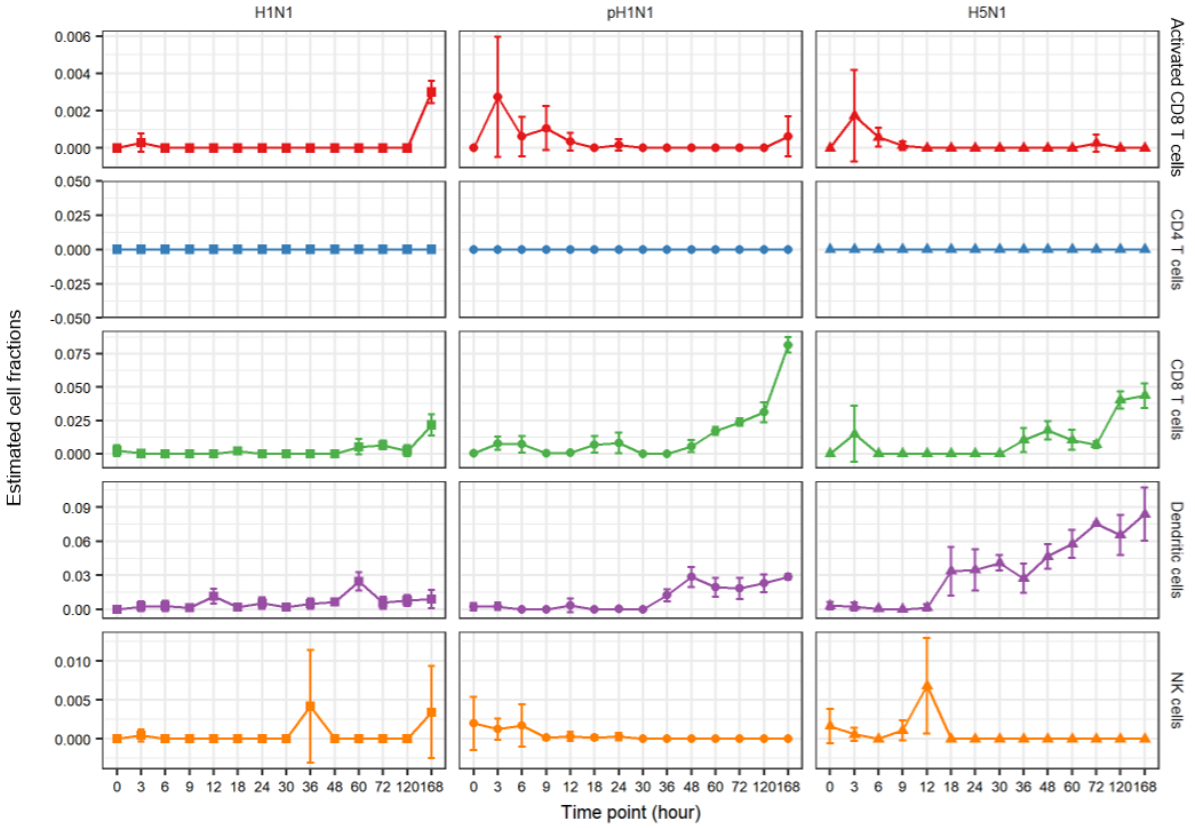


Figure S7. Estimated fractions of diverse cell types across time using MLLSR.

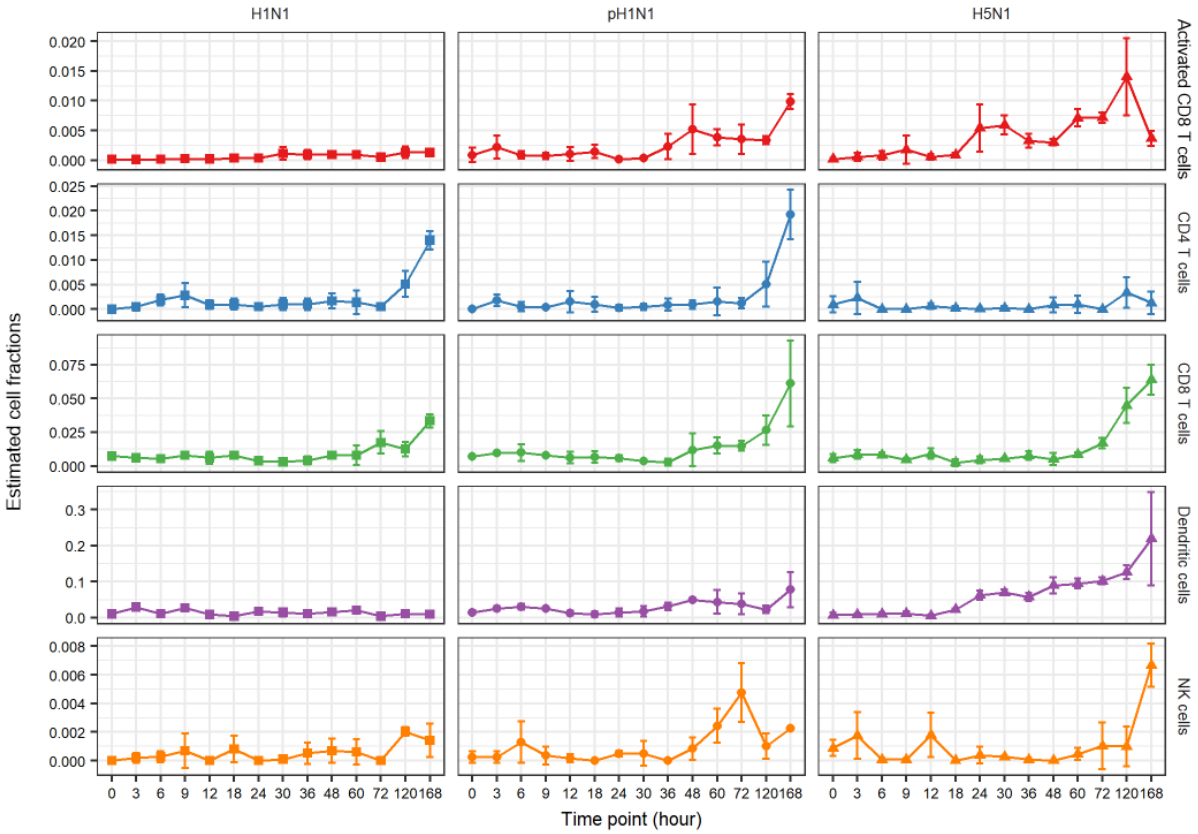


Figure S8. Estimated fractions of diverse cell types across time using CIBERSORT.

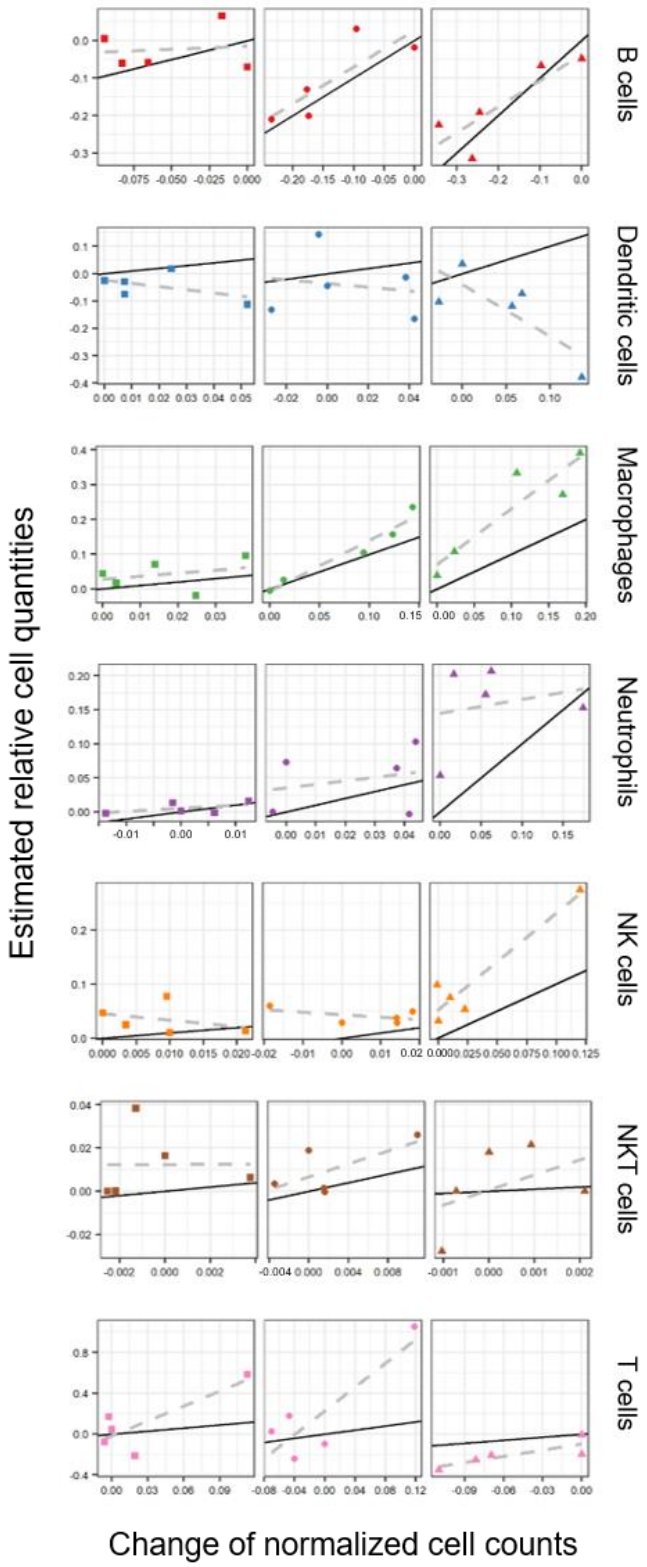


Figure S9. Estimated relative cell quantities by DCQ in comparison with the change in normalized cell counts for different cell types. The black line is y = x while the grey dashed line is regression.

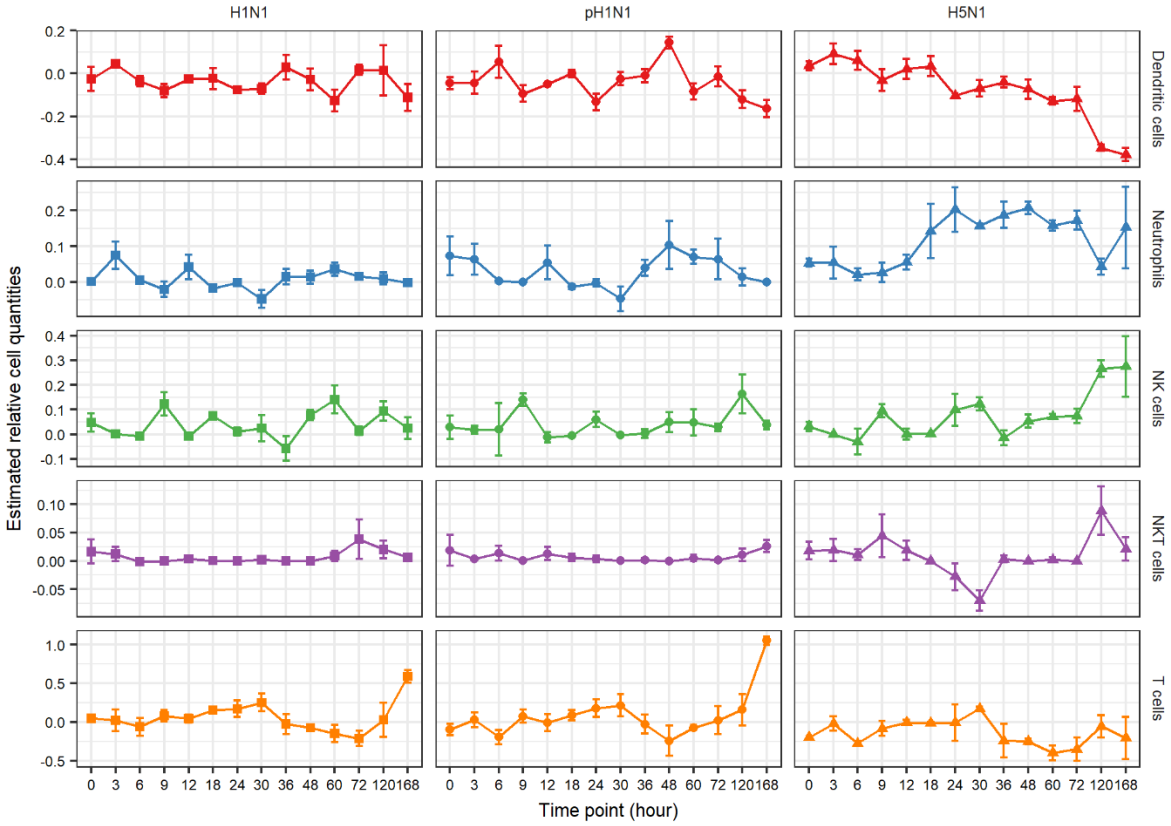


Figure S10. Estimated relative quantities of diverse cell types across time using DCQ.

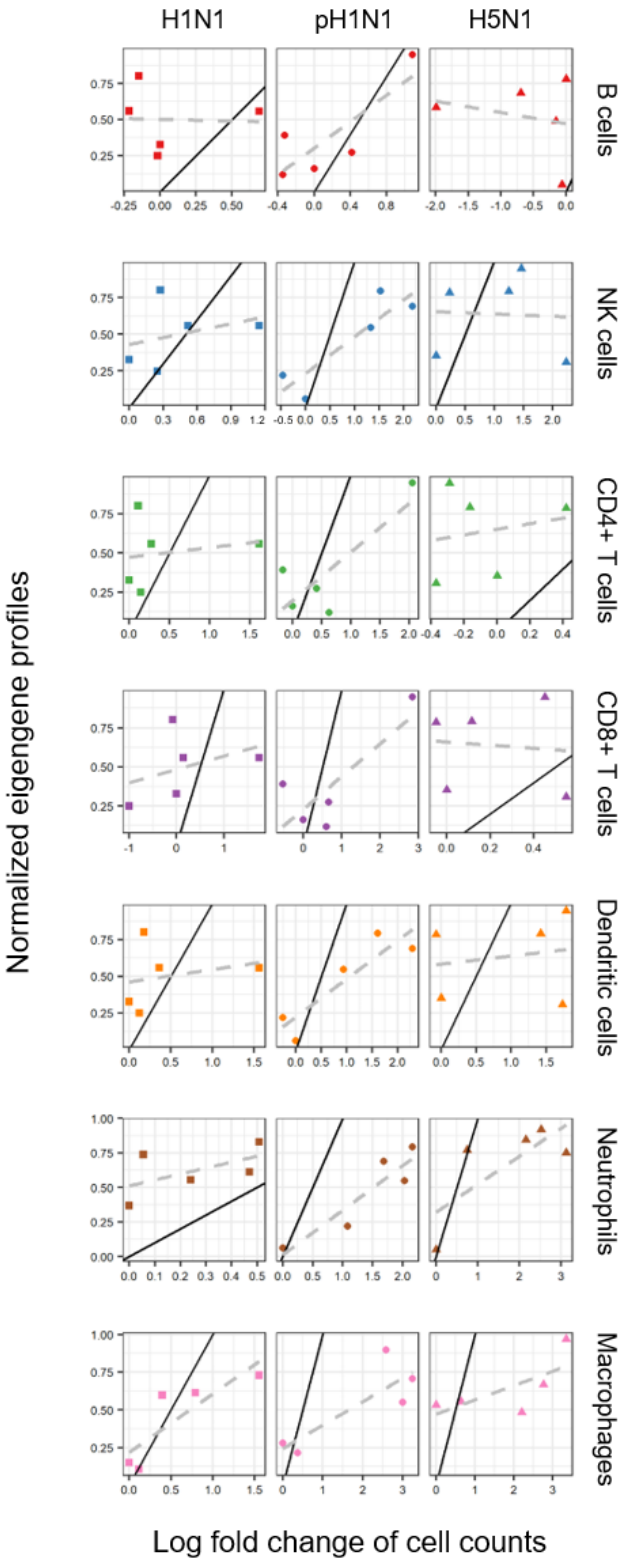


Figure S11. Normalized eigengene profiles by CTen & WGCNA in comparison with log fold change of cell counts measured by FACS for different cell types. The black line is y = x while the grey dashed line is regression.

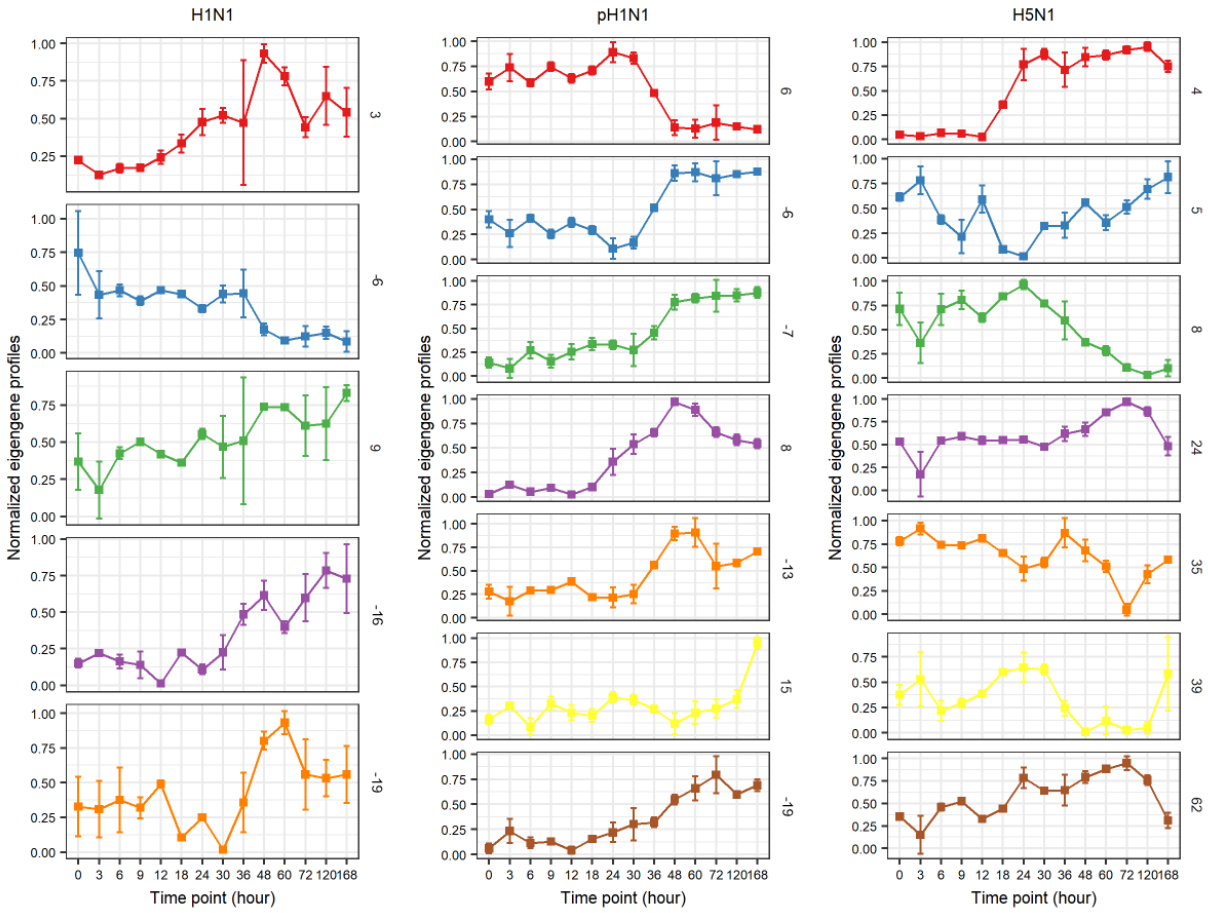


Figure S12. Normalized eigengene profiles of modules that are enriched in immune cells. Referring cell types for each module are listed in Supplementary Table 1. Negative submodules are denoted by an extra minus sign (Materials and Methods).

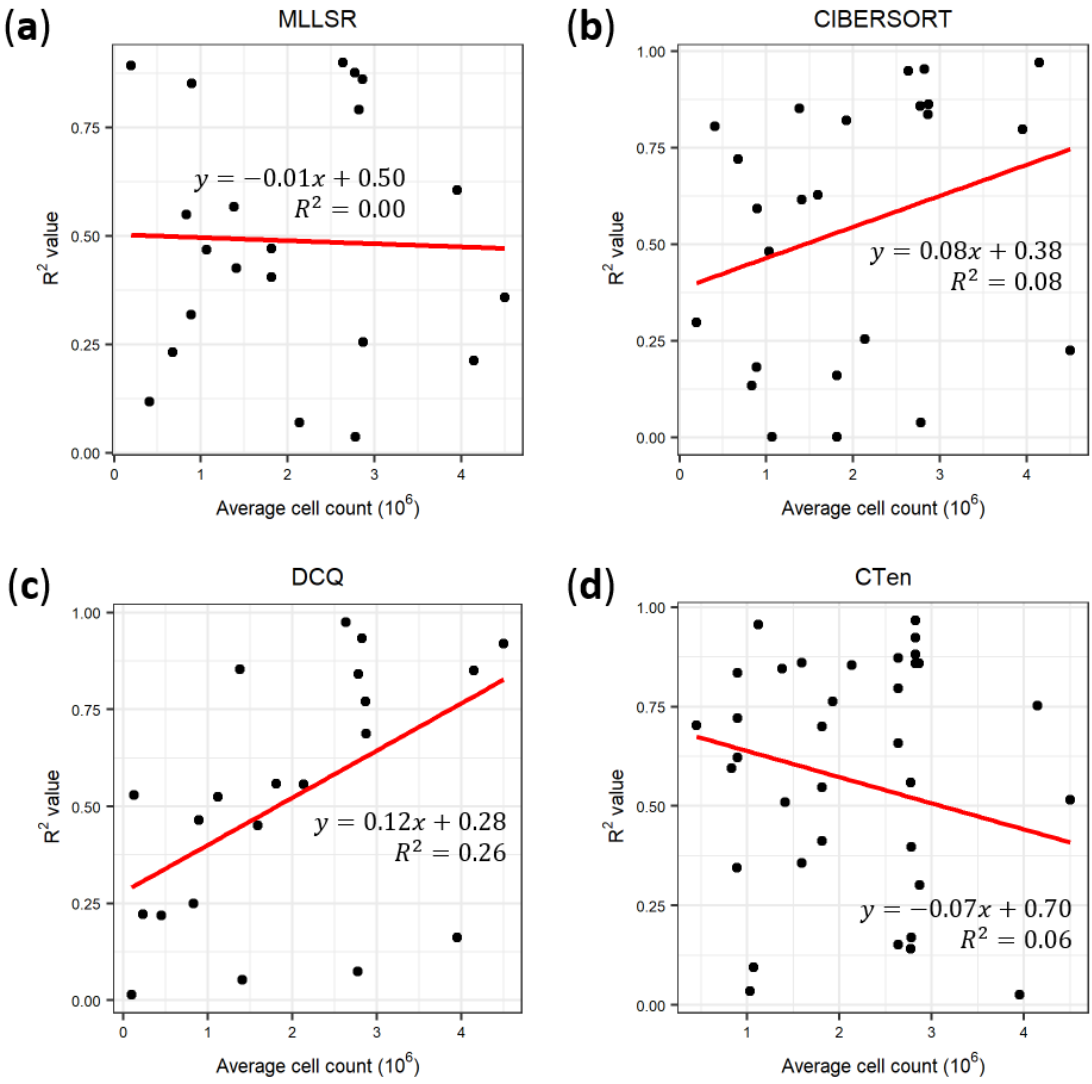


Figure S13. $R^2$ values obtained by comparing predicted cell quantities with measured cell counts are plotted against the average cell counts per cell type per sample cohort for each algorithm: (**a**) MLLSR, (**b**) CIBERSORT, (**c**) DCQ (*p*-value = 0.02), and (**d**) CTen. The red lines are regression lines with equations notated.

Table S1. Antibodies used in flow cytometry for each cell type

Table S2. $R^2$ values and NMSE obtained from comparing cell counts predicted by 4 algorithms (MLLSR, CIBERSORT, DCQ, CTen) with flow cytometry data

Table S3. Modules obtained from WGCNA that are enriched in immune cell subsets per virus strain

Table S4. Genes are sorted by FDR values calculated based on adjusted expression $\boldsymbol{g}$, adjusted expression $\boldsymbol{e}$ & standard differential expression analysis. Virus proteins that interact with the associated protein of a gene are obtained from VirHostNet2 [45].

Table S5. Functional annotations are obtained from applying significant genes (FDR < $1\times10^{-4}$ for at least 2 time points) to DAVID [43,44] based on adjusted gene expression $\boldsymbol{g}$.

Table S6. Functional annotations are obtained from applying significant genes (FDR < $1\times10^{-4}$ for at least 2 time points) to DAVID [43,44] based on standard DE analysis.

Table S7. Functional annotations are obtained from applying significant genes (FDR < $1\times10^{-4}$ for at least 2 time points) to DAVID [43,44] based on adjusted gene expression $\boldsymbol{e}$.