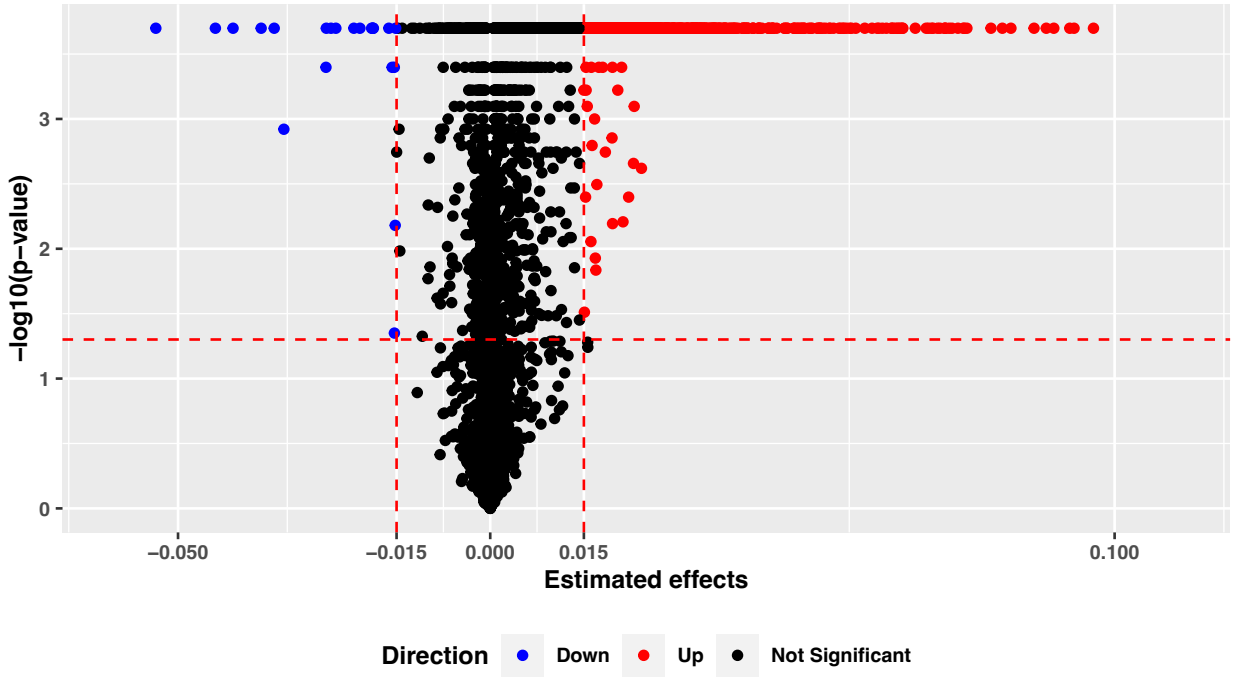
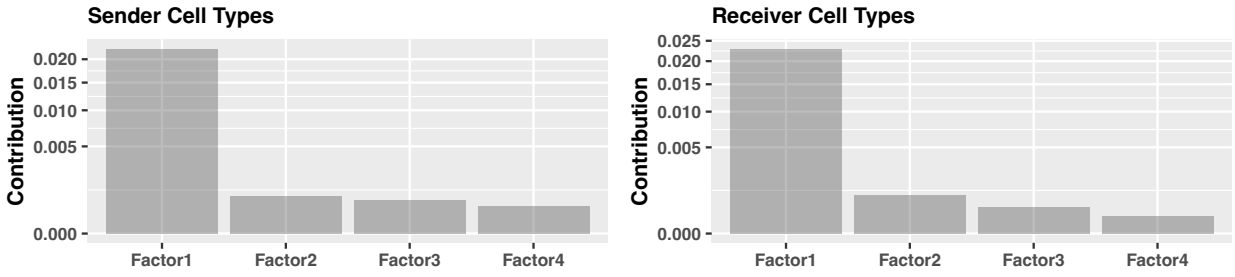
Supplementary Figures

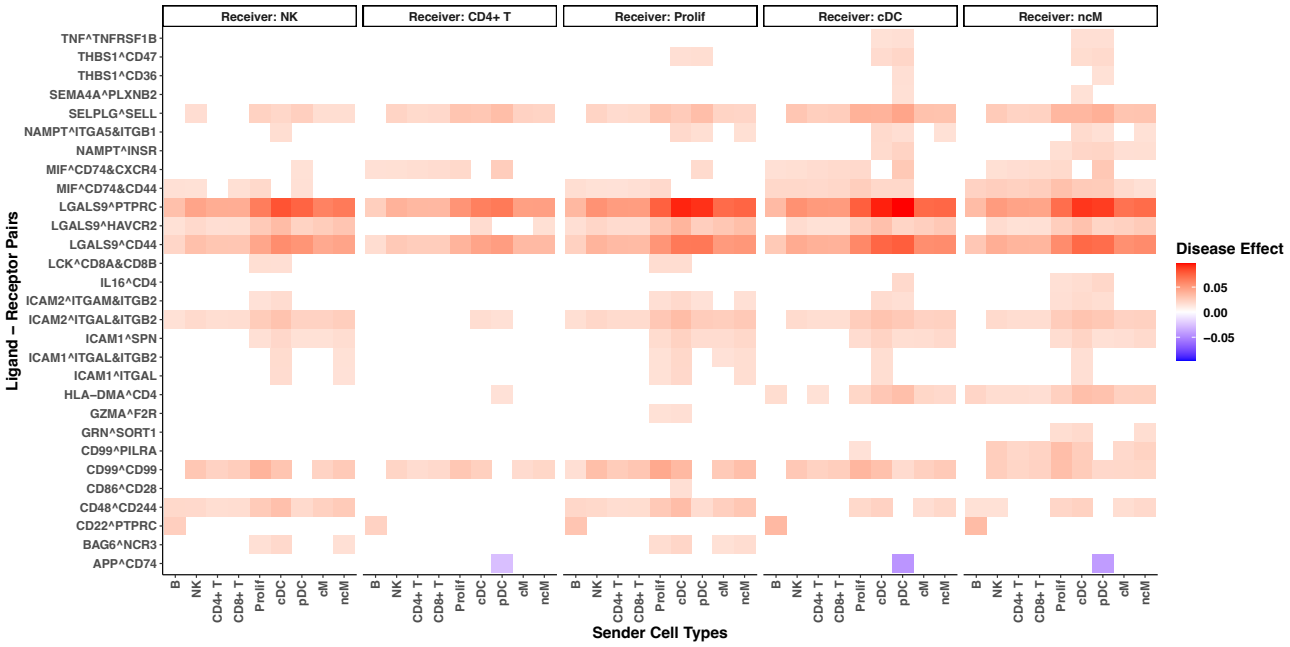
Supplementary Figure 1. Significance levels of the estimated disease effects in SLE dataset. Significance levels are represented as -log10(p-values). Significant estimated disease effects, with p-values < 0.05 and magnitudes > 0.015, are colored blue for negative effects and red for positive effects. Non-significant estimated disease effects are shown in black. The p-values are two-sided p-values obtained using 4,999 iterations of bootstrap resampling, with the minimum attainable p-value being $1/(4999 + 1) = 2 \times 10^{-4}$.



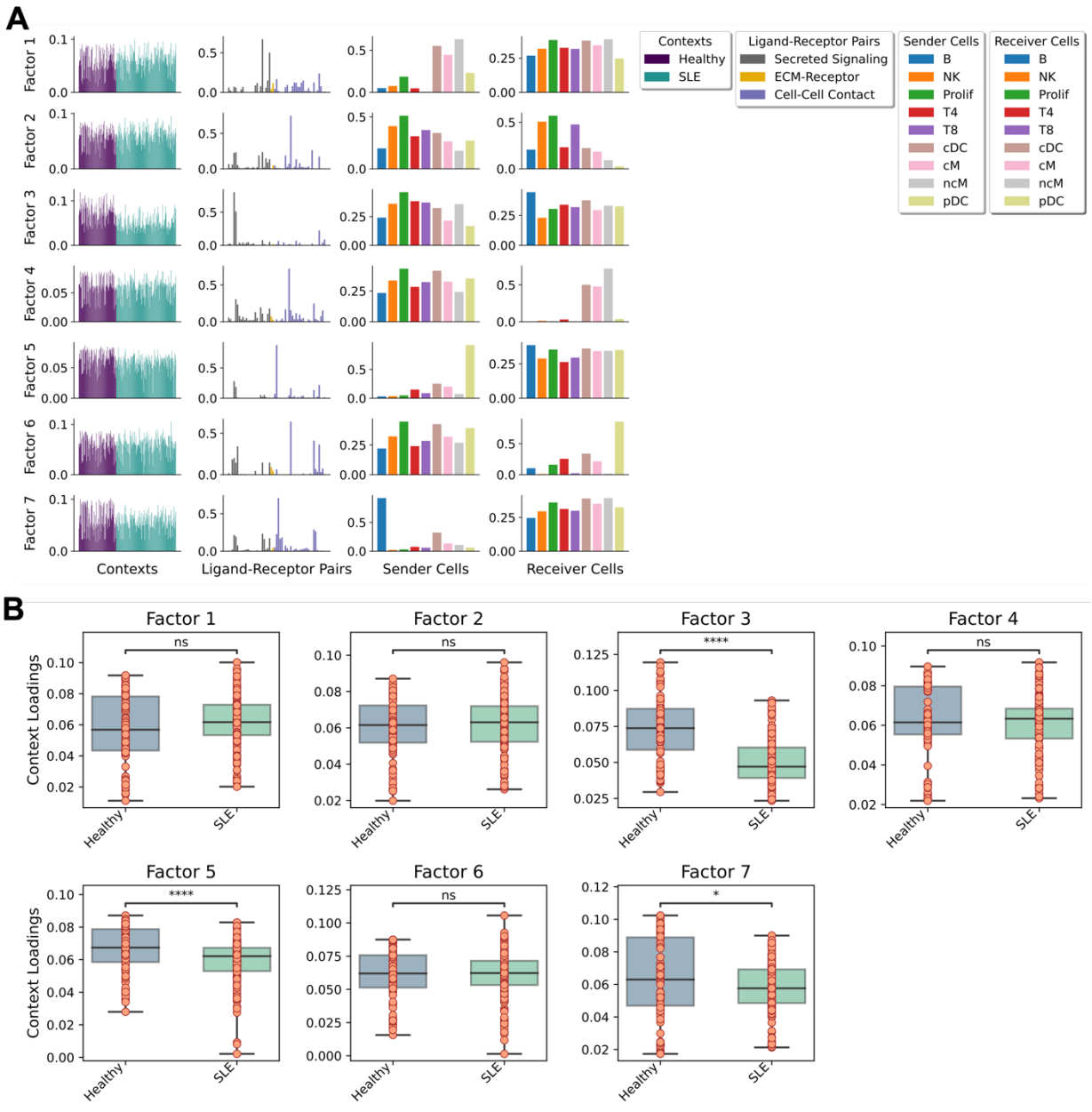
Supplementary Figure 2. Contributions of the factors of sender cell types (A) and receiver cell types (B) in SLE dataset.



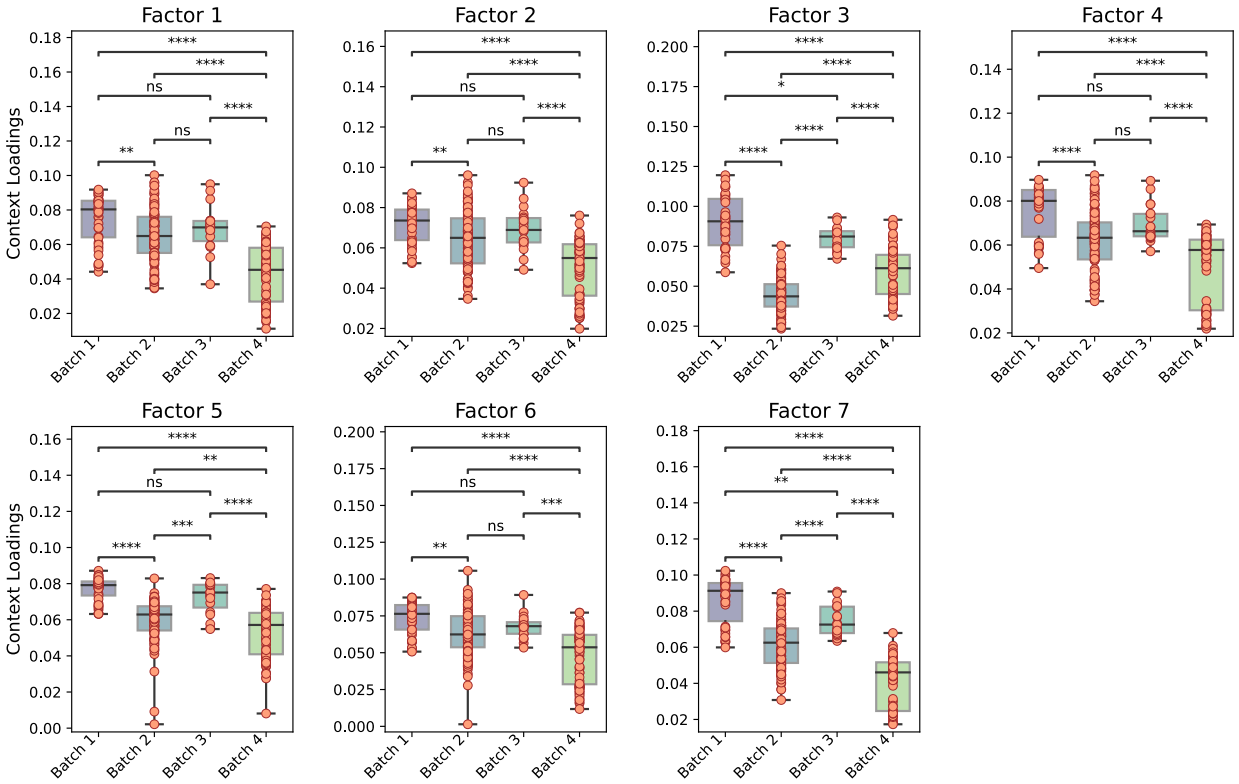
Supplementary Figure 3. Estimated significant disease effects with p-values < 0.05 and magnitudes > 0.015 for communication events with NK, CD4^{+} T, Prolif, cDC, and ncM cells as receiver cell types in SLE dataset. Positive disease effects are colored in red while negative disease effects are colored in blue.



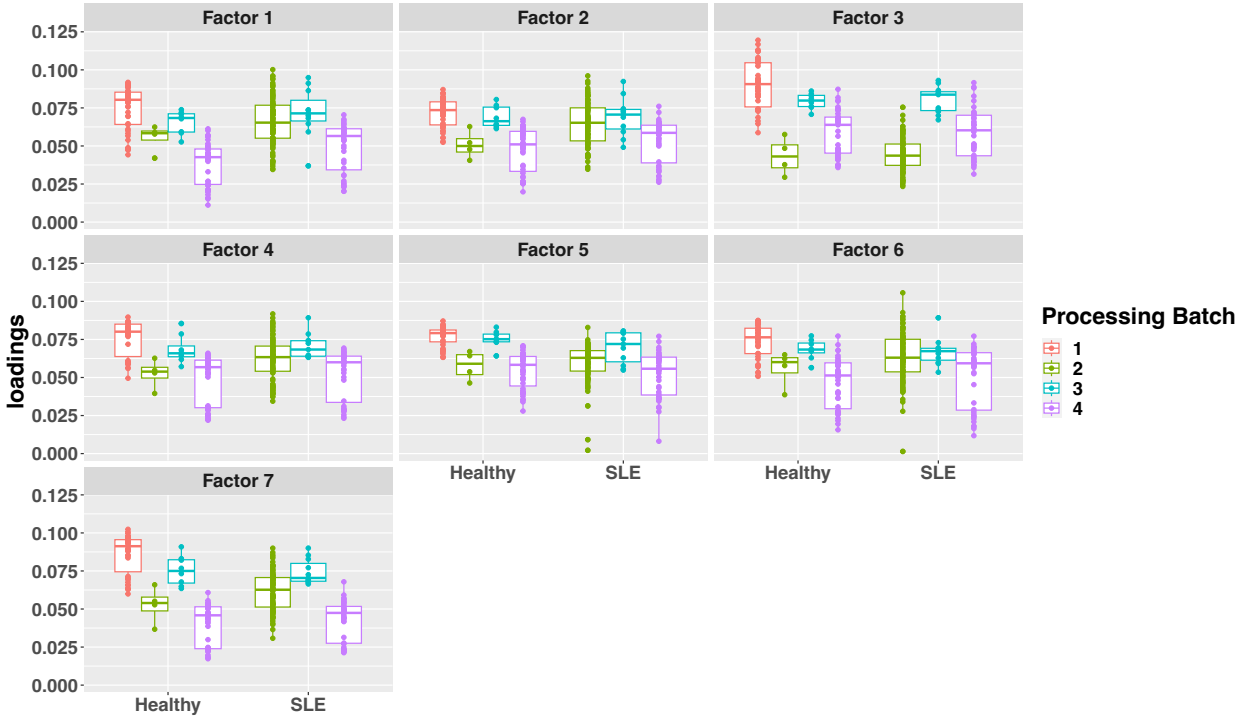
Supplementary Figure 4. Tensor-cell2cell decomposition results of the SLE data. (A) Bar plots of the decomposed loadings of factors per tensor dimension. (B) Box-plot to compare the loadings of healthy controls versus SLE patients for each factor. Factors 3, 5, and 7 are significantly associated with SLE with p-values < 0.05. P-values were calculated using two-sample t-test. P-values < 10^{-4} are displayed as "****"; p-values < 10^{-3} are displayed as "***"; p-values < 10^{-2} are displayed as "**"; p-values < 0.05 are displayed as "*", and p-values < 1 are displayed as "ns".



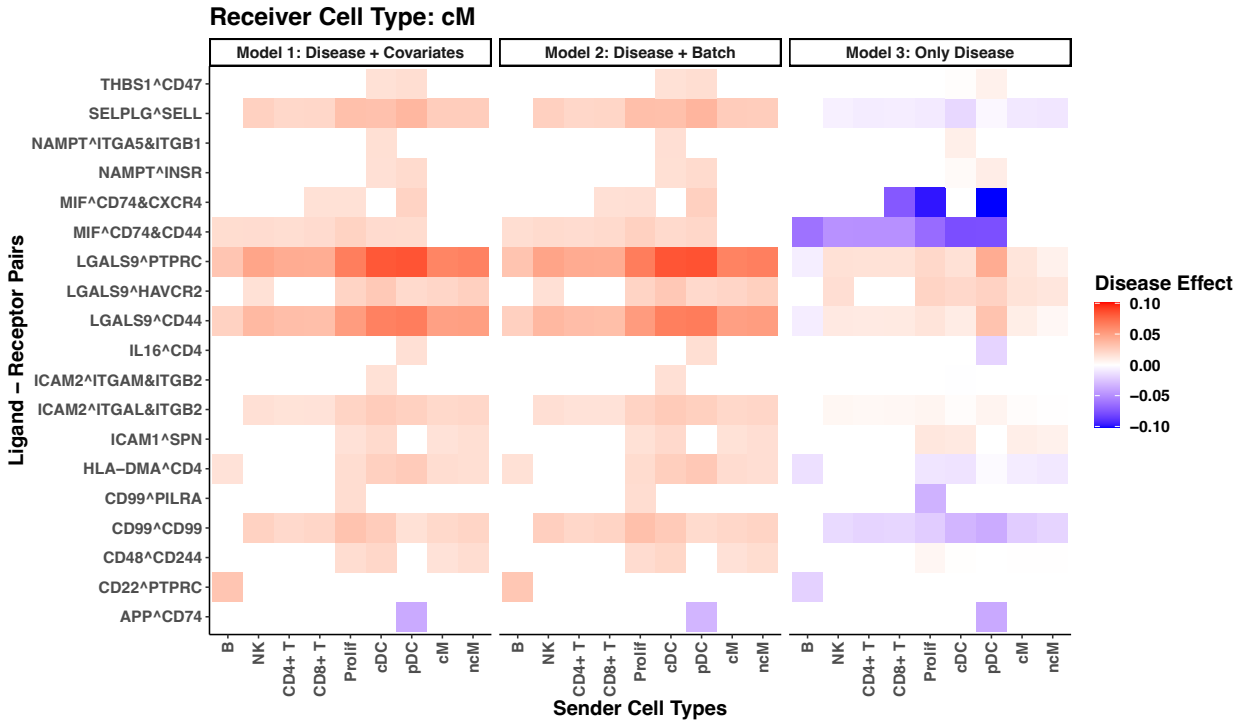
Supplementary Figure 5. Associations between factors identified by Tensor-cell2cell and batches. Box plots comparing the loadings of subjects in different batches for each Tensor-cell2cell factor. All factors are significantly associated with batches. P-values were calculated using two-sample t-test. P-values < 10^{-4} are displayed as "****"; p-values < 10^{-3} are displayed as "***"; p-values < 10^{-2} are displayed as "**"; p-values < 0.05 are displayed as "*", and p-values < 1 are displayed as "ns".



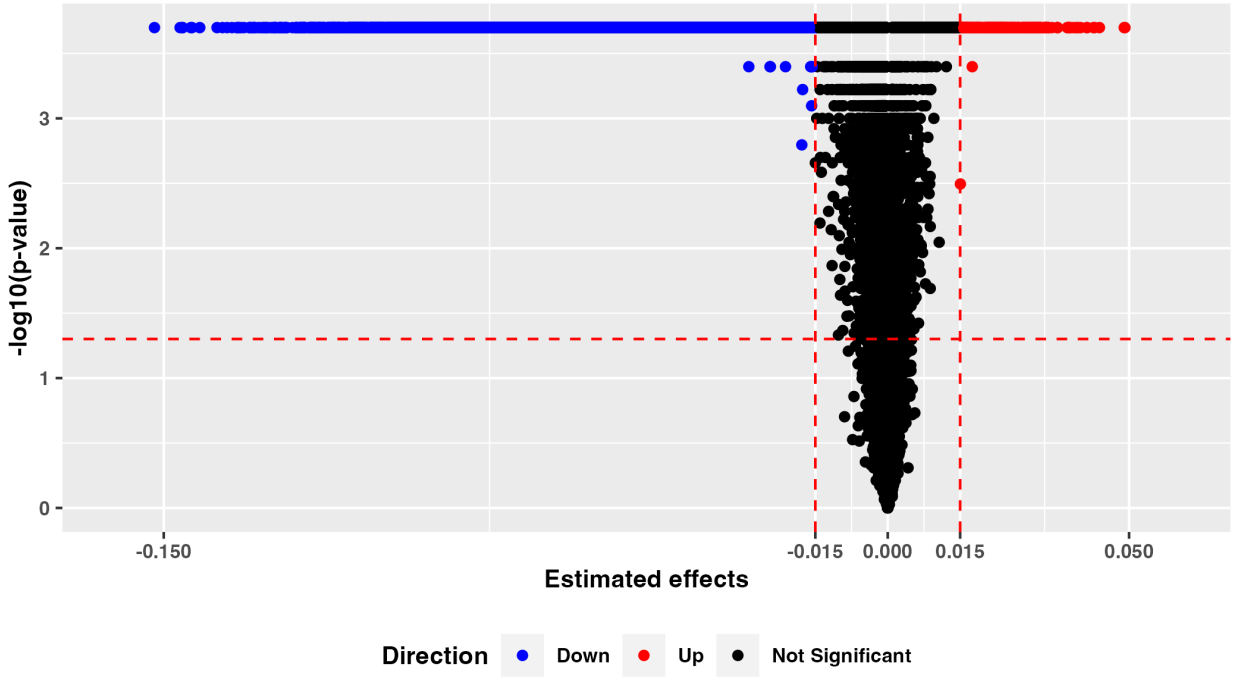
Supplementary Figure 6. Associations between the factors identified by Tensor-cell2cell and SLE disease status across batches. Box-plots to compare the loadings of healthy controls versus SLE patients for each Tensor-cell2cell factor, with colors representing the processing batches.



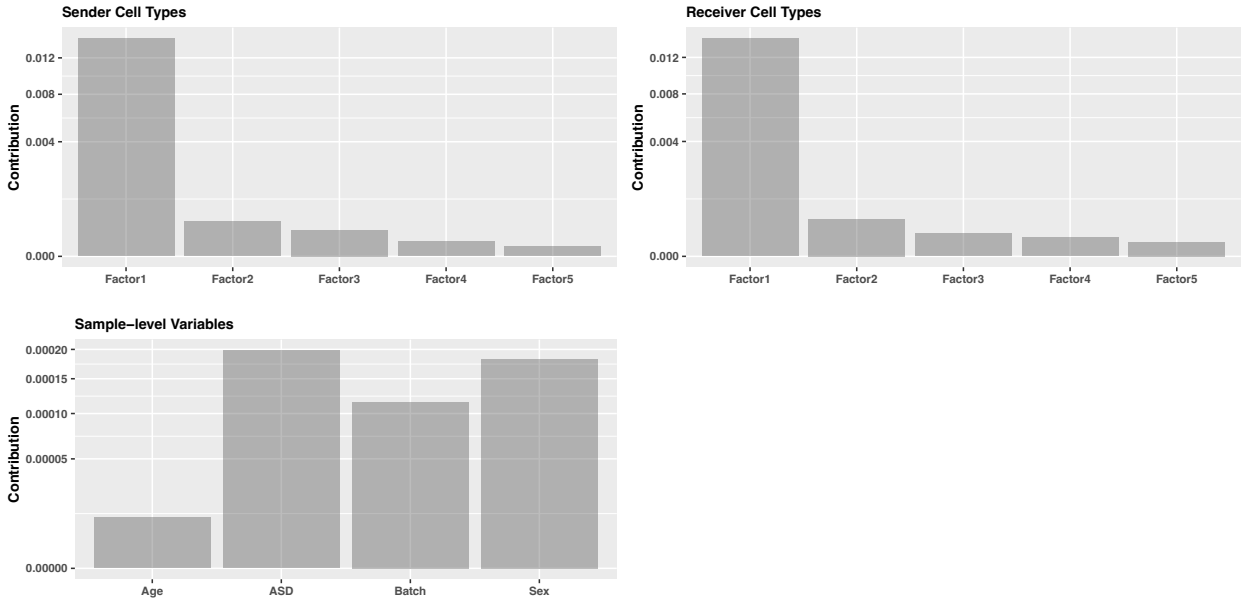
Supplementary Figure 7. Significant disease effects for CCC events with cM as receiver cell type estimated from three models: Model 1 uses all available variables, including disease status and other covariates such as age, gender, ancestry, and batch; Model 2 uses only disease status and batch variables; Model 3 uses only disease status. Positive disease effects are colored in red while negative disease effects are colored in blue.



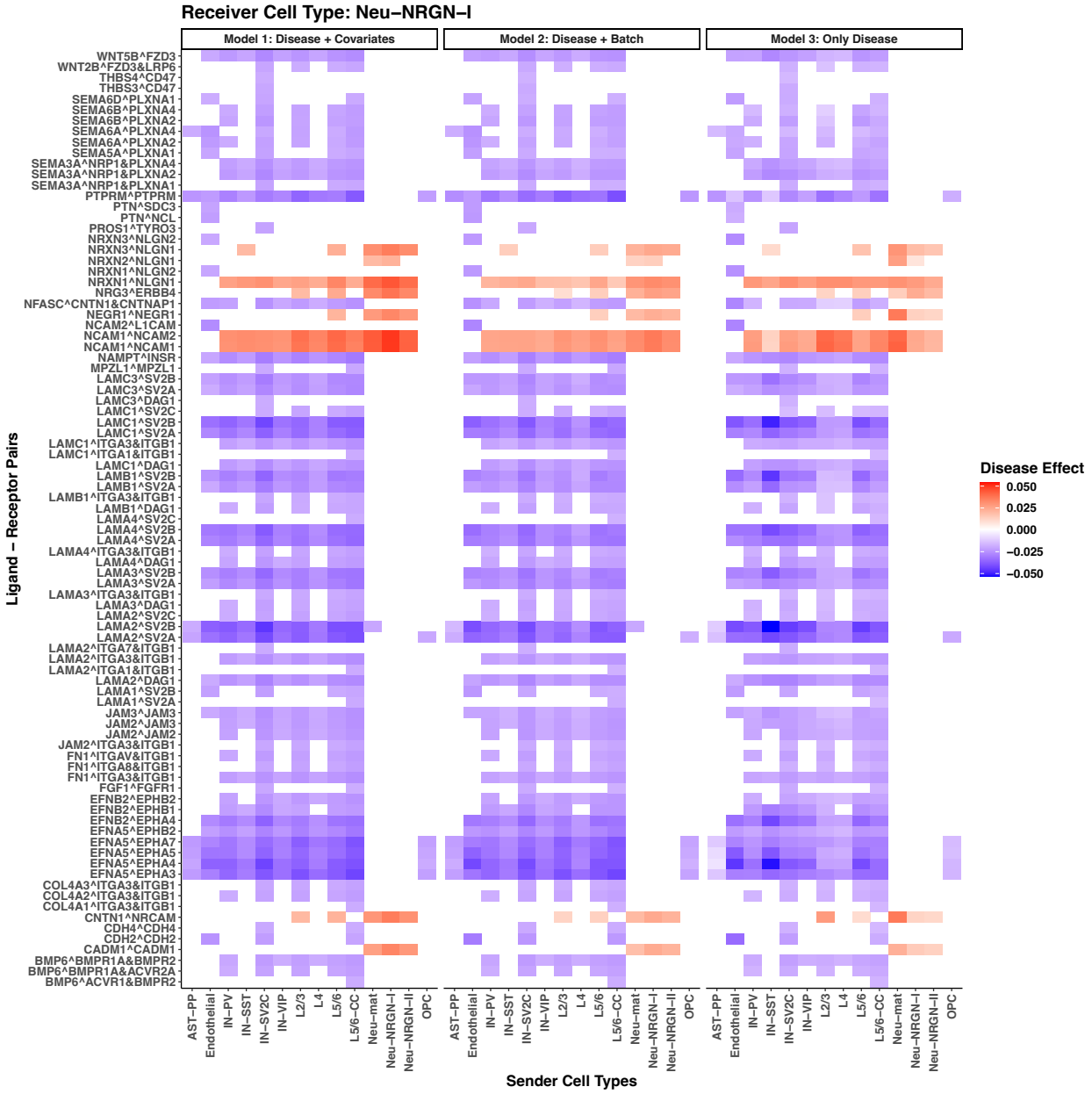
Supplementary Figure 8. Significance levels of the estimated disease effects in the ASD dataset. Significance levels are represented as -log10(p-values). Significant estimated disease effects, with p-values < 0.05 and magnitudes > 0.015, are colored blue for negative effects and red for positive effects. Non-significant estimated disease effects are shown in black. The p-values are two-sided p-values obtained using 4,999 iterations of bootstrap resampling, with the minimum attainable p-value being $1/(4999 + 1) = 2 \times 10^{-4}$.



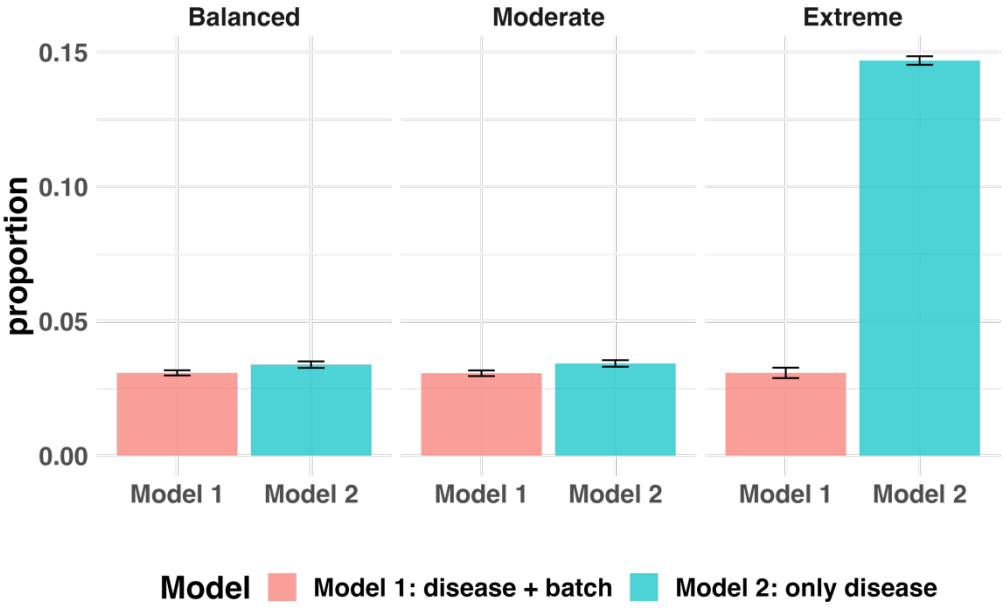
Supplementary Figure 9. Contributions of factors of sender cell types (A), receiver cell types (B), and sample-level variables (C) in the ASD dataset.



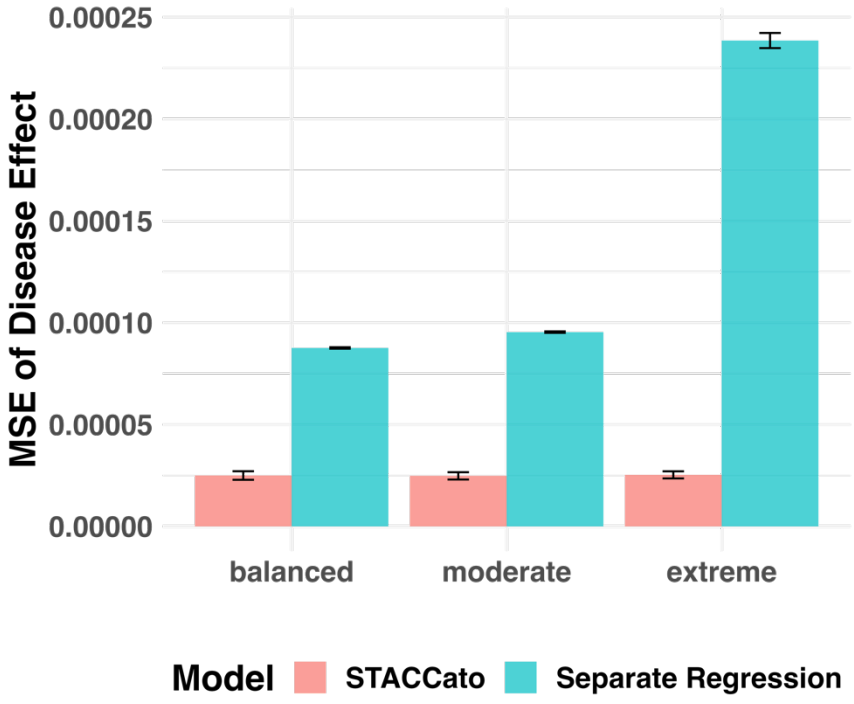
Supplementary Figure 10. Significant disease effects for CCC events with Neu-NRGN-I as receiver cell type estimated from three models: Model 1 uses all available variables, including disease status and other covariates such as age, gender, and batch; Model 2 uses only disease status and batch variables; Model 3 uses only disease status. Positive disease effects are colored in red while negative disease effects are colored in blue. The presented CCC events are those with the top 500 largest magnitudes of disease effects and a bootstrapping p-value < 0.05 in Model 1.



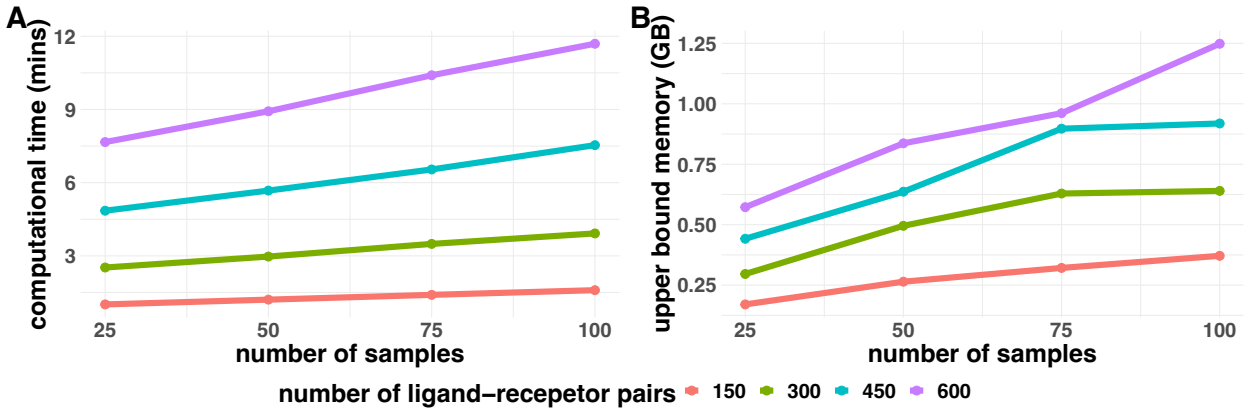
Supplementary Figure 11. STACCato simulation results: proportion of estimated disease effects with directions opposite to the assumed direction in balanced, moderate unbalanced, and extreme unbalanced scenarios. The bar plots show the mean proportions across 100 simulations from Model 1 considering disease status and batch variables (red bars) and Model 2 considering disease status only (green bars), with black error bars showing standard errors.



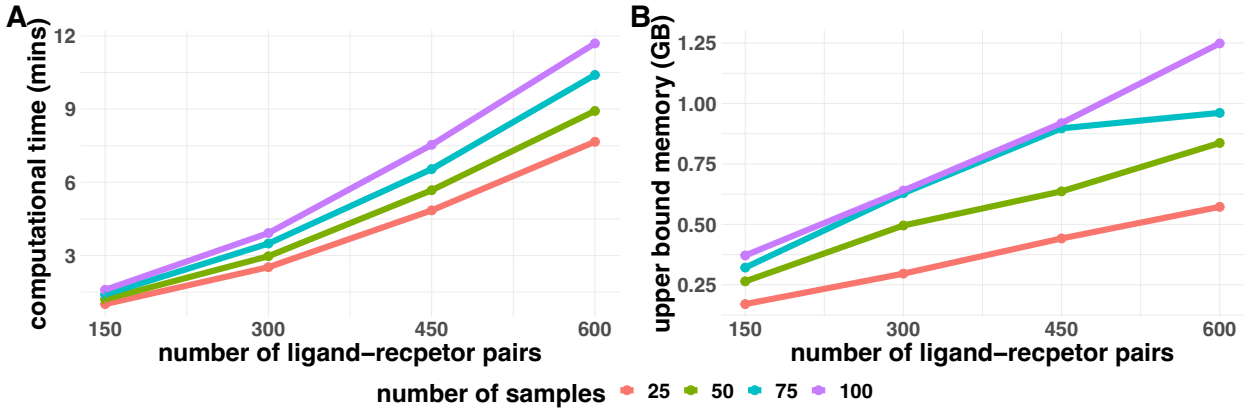
Supplementary Figure 12. MSEs of estimated disease effects by STACCato versus separate regression in balanced, moderate unbalanced, and extreme unbalanced simulation scenarios. The bar plot shows the average MSEs across 100 simulations from STACCato (red bars) and separate regression (green bars) with black error bars showing standard errors. Both STACCato and the separate regression used the full sample-level information including intercept, disease status, and batch variables.



Supplementary Figure 13. Time and memory usage of 99 iterations of bootstrapping resampling in simulated datasets with 10 sender and receiver cell types and 10 sample-level covariates, across different number of samples. (A): Computational times are in minutes (mins); (B): Upper bounds of memory usages are in gigabytes (GB). X-axis shows simulation scenarios with different numbers of samples. Color represents different total numbers of ligand-receptor pairs.



Supplementary Figure 14. Time and memory usage of 99 times of bootstrapping resampling in simulated datasets with 10 sender and receiver cell types and 10 sample-level covariates, across different number of ligand-receptor pairs. (A): Computational times are in minutes (mins); (B): Upper bounds of memory usages are in gigabytes (GB). X-axis shows simulation scenarios with different numbers of ligand-receptor pair. Color represents different numbers of samples.



Supplementary Tables

Supplementary Table 1. The contingency table displays the number of healthy controls and SLE patients in each processing batch of the SLE dataset. We reduced the SLE dataset down to one sample per subject by selecting the sample with largest number of cells and only included the 251 samples with Asian or European ancestry and containing 9 main cell types (B, NK, Prolif, $CD4^+$ T cells, $CD8^+$ T cells, cM, ncM, cDC, and pDC cells).

	Batch 1	Batch 2	Batch 3	Batch 4
Healthy controls	42	4	8	43
SLE patients	0	103	11	40

Supplementary Table 2. The contingency table displays the number of healthy controls and ASD patients in each processing batch of the ASD dataset.

	Batch 1	Batch 2
Healthy controls	5	5
ASD patients	5	8