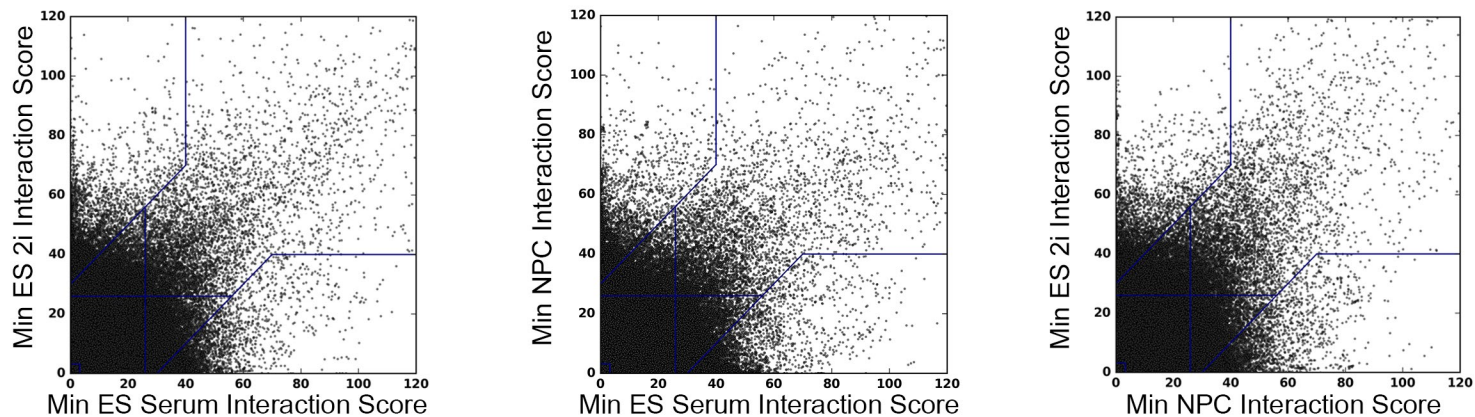


**A**

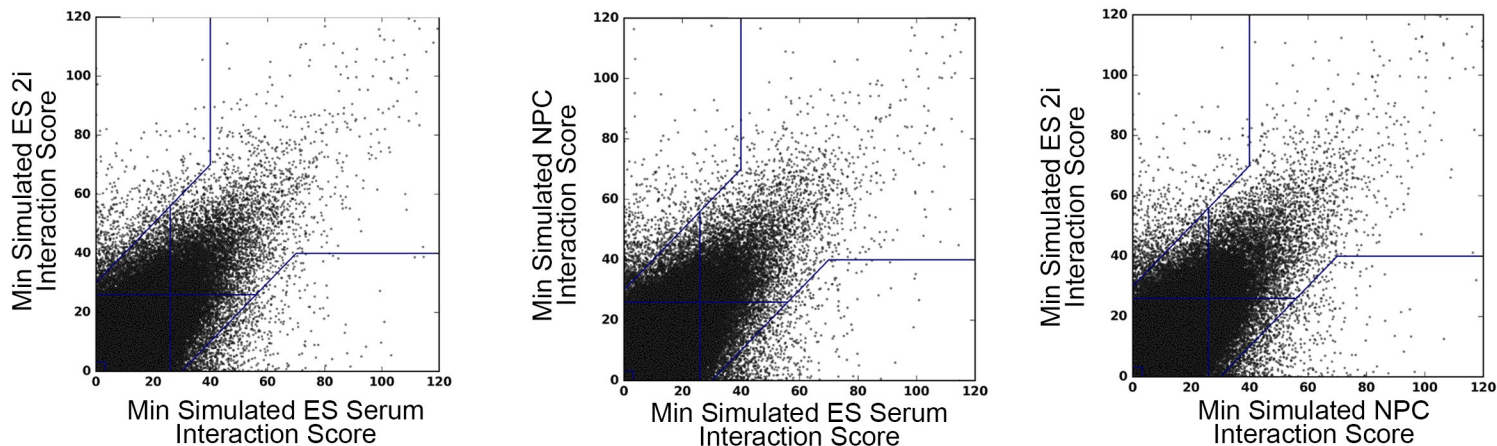


**B**

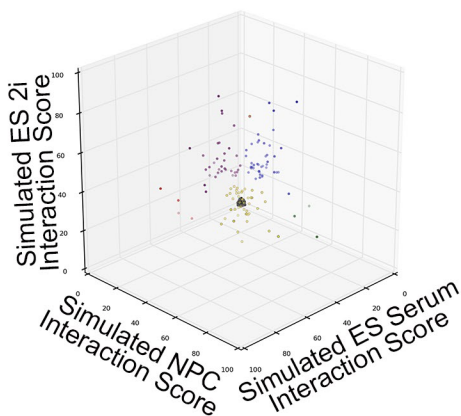
| Cell Type | Correlation Calculation | Background Normalized Counts Correlations | Simulated NPC Reps |                      | Simulated ES Serum Reps    |          |                            |          |
|-----------|-------------------------|---|--------------------|----------------------|----------------------------|----------|----------------------------|----------|
|           |                         |   | Looping Class      | Real Data Loop Count | Simulated Data Loop Count* | FDR      | Simulated Data Loop Count* | FDR      |
| ES 2i     | Pearson's               | 0.72764936                                | 2i + Serum         | 374                  | 44.181                     | 11.8131  | 38.137                     | 10.19706 |
|           | Spearman's              | 0.689918988                               | NPC + 2i           | 530                  | 44.114                     | 8.323396 | 37.853                     | 7.142075 |
| ES Serum  | Pearson's               | 0.745865553                               | Serum + NPC        | 104                  | 43.911                     | 42.22212 | 38.152                     | 36.68462 |
|           | Spearman's              | 0.726672268                               | NPC only           | 712                  | 2.384                      | 0.334831 | 1.6                        | 0.224719 |
| NPC       | Pearson's               | 0.637227701                               | 2i only            | 451                  | 2.238                      | 0.496231 | 1.583                      | 0.350998 |
|           | Spearman's              | 0.606833588                               | Serum only         | 347                  | 2.271                      | 0.654467 | 1.577                      | 0.454467 |

\*Reported as the average number of classified interactions across 1000 simulations

**C**



**D**



**Supplemental Figure S8. Thresholding Interaction Scores to Achieve Reasonable False Discovery Rates. (A)** 2D Scatterplot of the minimum interaction scores across the two replicates of each cell type for all bin-bin pairs. Blue lines show applied thresholds. **(B)** Tables of expected-corrected interaction frequency correlations (left) and real 5C data pixel counts within looping classes compared to simulated pixel count and false discovery rate (FDR) within looping classes of simulated ES serum and NPC replicates (right). **(C)** 2D scatterplot of the minimum interaction scores across the two replicates of each simulated cell type for all bin-bin pairs. Blue lines denote applied thresholds. **(D)** 3D scatterplot of the classified interactions from the first NPC simulation. Related to Figure 3.