

# Single-cell Pairwise Relationships Untangled by Composite Topic models

Park Lab

11:16:05 AM, Jun 20, 2022

## Cell topic analysis

Multinomial-Dirichlet:

$$p(\mathbf{y}_i | \mathbf{q}_i) = \frac{(\sum_g Y_{ig})!}{\prod_g Y_{ig}!} \prod_g q_{ig}^{Y_{ig}}$$

$$\mathbf{q}_i \sim \text{Dir}(\mathbf{q}_i | \rho_i) = \frac{\Gamma(\sum_g \rho_{ig})}{\prod_g \Gamma(\rho_{ig})} \prod_g q_{ig}^{\rho_{ig}-1}$$

Single-cell generative model:

$$p(\mathbf{x}_j | \cdot) = \frac{\Gamma(\sum_g \lambda_{jg})}{\sum_g \Gamma(\lambda_{jg})} \frac{\Gamma(\sum_g \lambda_{jg} + X_{jg})}{\sum_g \Gamma(\lambda_{jg} + X_{jg})}$$

where

$$\lambda_{jg} = \exp \left( \sum_{t=1}^T \theta_{jt} (\beta_{tg} + \delta_g) \right)$$

Bayesian regularization of the model parameters

$$\beta_{tg} \sim \mathcal{N}(0, 1)$$

Total Expected log-likelihood Lower-bound (ELBO):

$$\begin{aligned}
\frac{J}{n} &= \frac{1}{n} \sum_{i=1}^n \log p(\mathbf{x}_i | \theta_i(\mathbf{z}_i), \beta) \\
&\quad + \frac{1}{n} \sum_{i=1}^n \sum_{t=1}^T D_{\text{KL}}(q(z_{it}) \| p(z_{it})) \\
&\quad + \frac{1}{n} \sum_{t=1}^T \sum_{g=1}^G D_{\text{KL}}(q(\beta_{tg}) \| p(\beta_{tg})) \\
&\approx \frac{1}{B} \sum_{i=1}^B \log p(\mathbf{x}_i | \theta_i(\mathbf{z}_i), \beta) \\
&\quad + \frac{1}{B} \sum_{i=1}^B \sum_{t=1}^T D_{\text{KL}}(q(z_{it}) \| p(z_{it})) \\
&\quad + \frac{1}{n} \sum_{t=1}^T \sum_{g=1}^G D_{\text{KL}}(q(\beta_{tg}) \| p(\beta_{tg}))
\end{aligned}$$

where  $B$  is the mini-batch size.

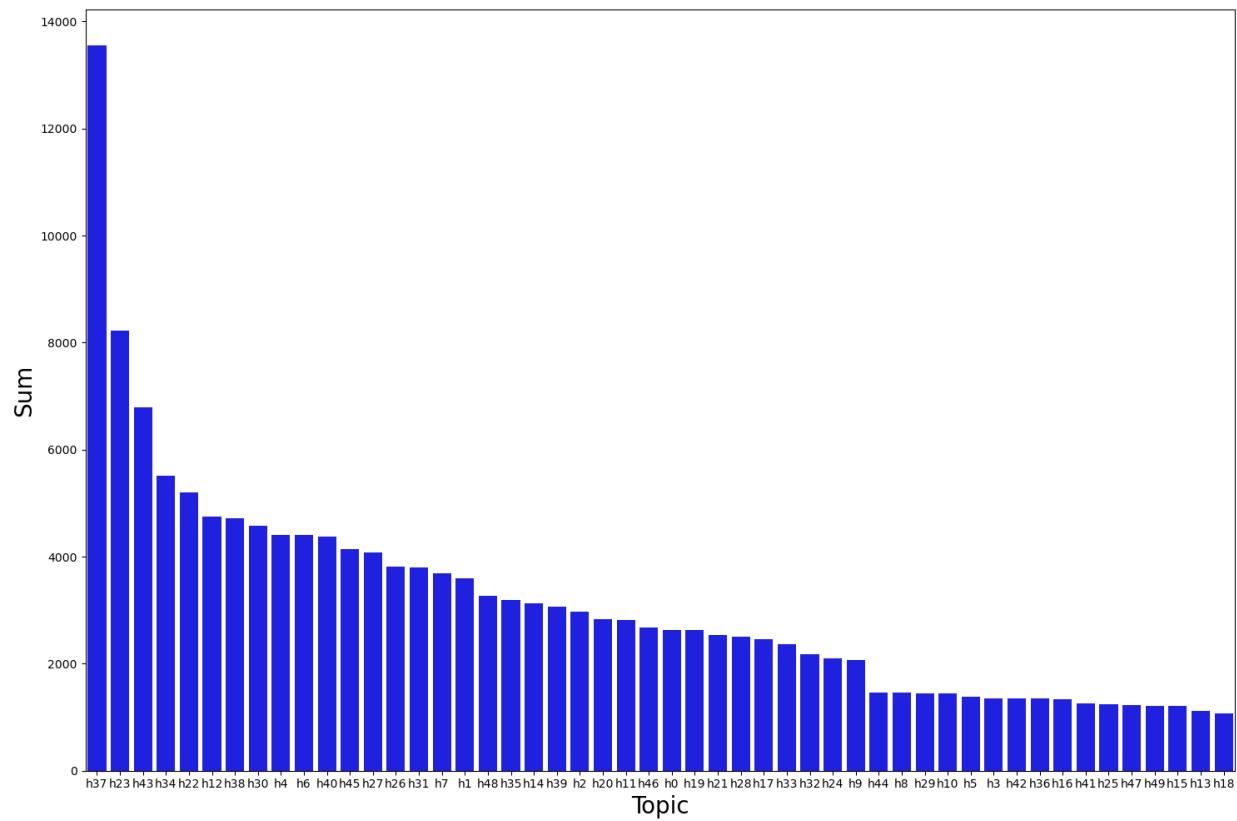


Figure 1: Topic sum

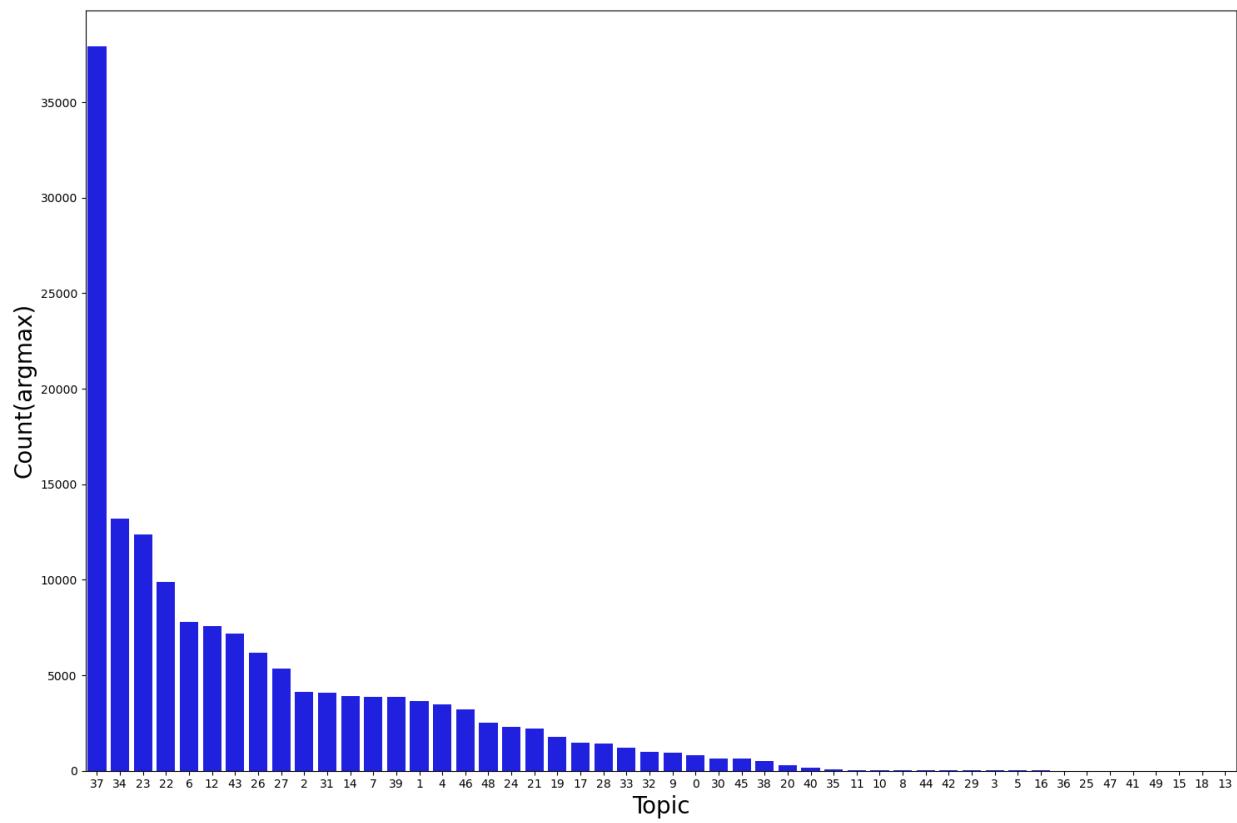


Figure 2: Topic argmax

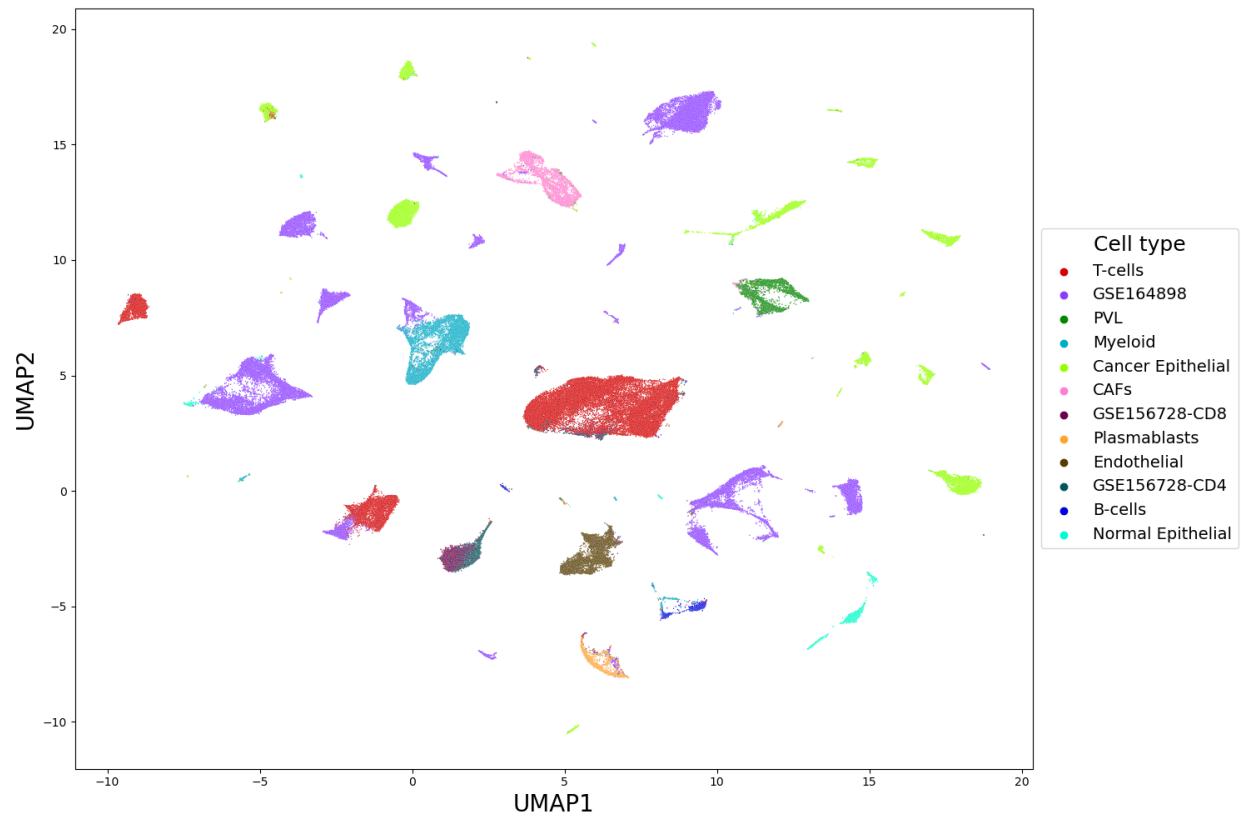


Figure 3: UMAP cell-type

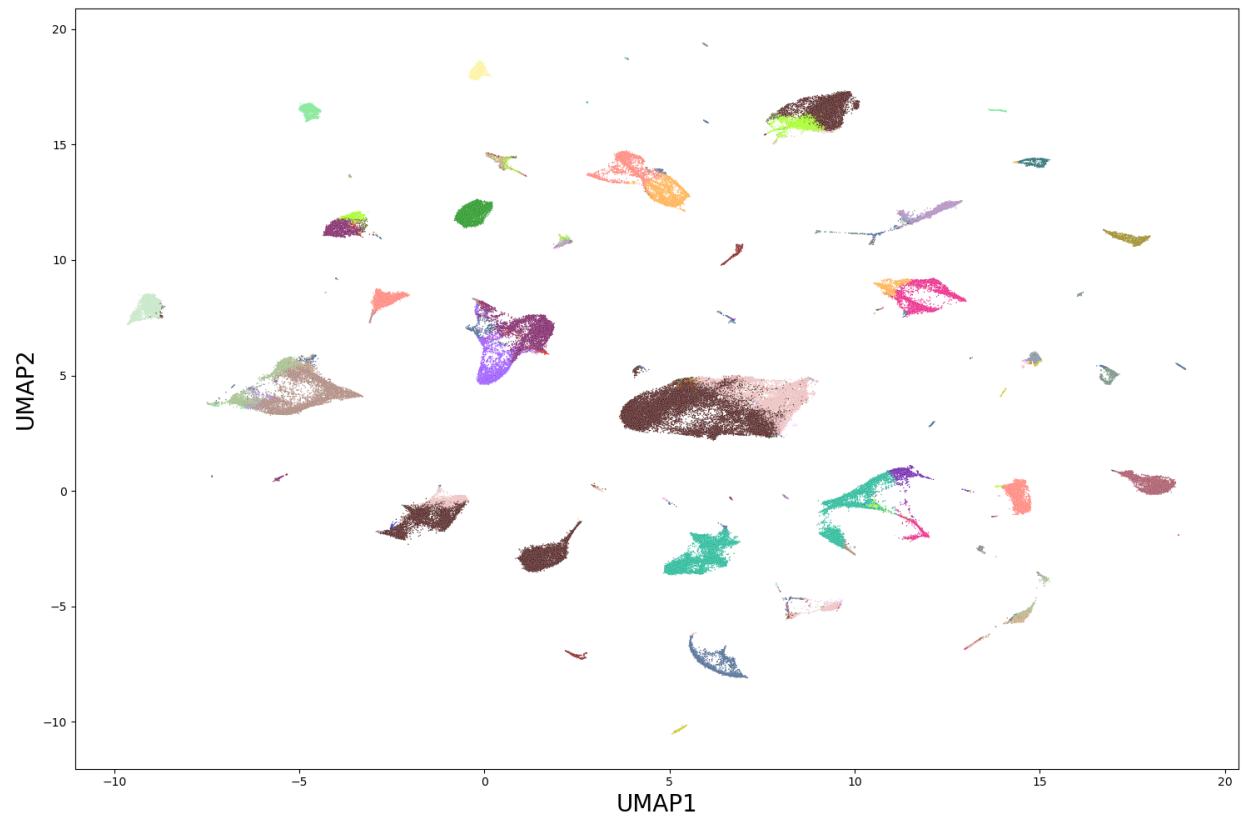


Figure 4: UMAP topic

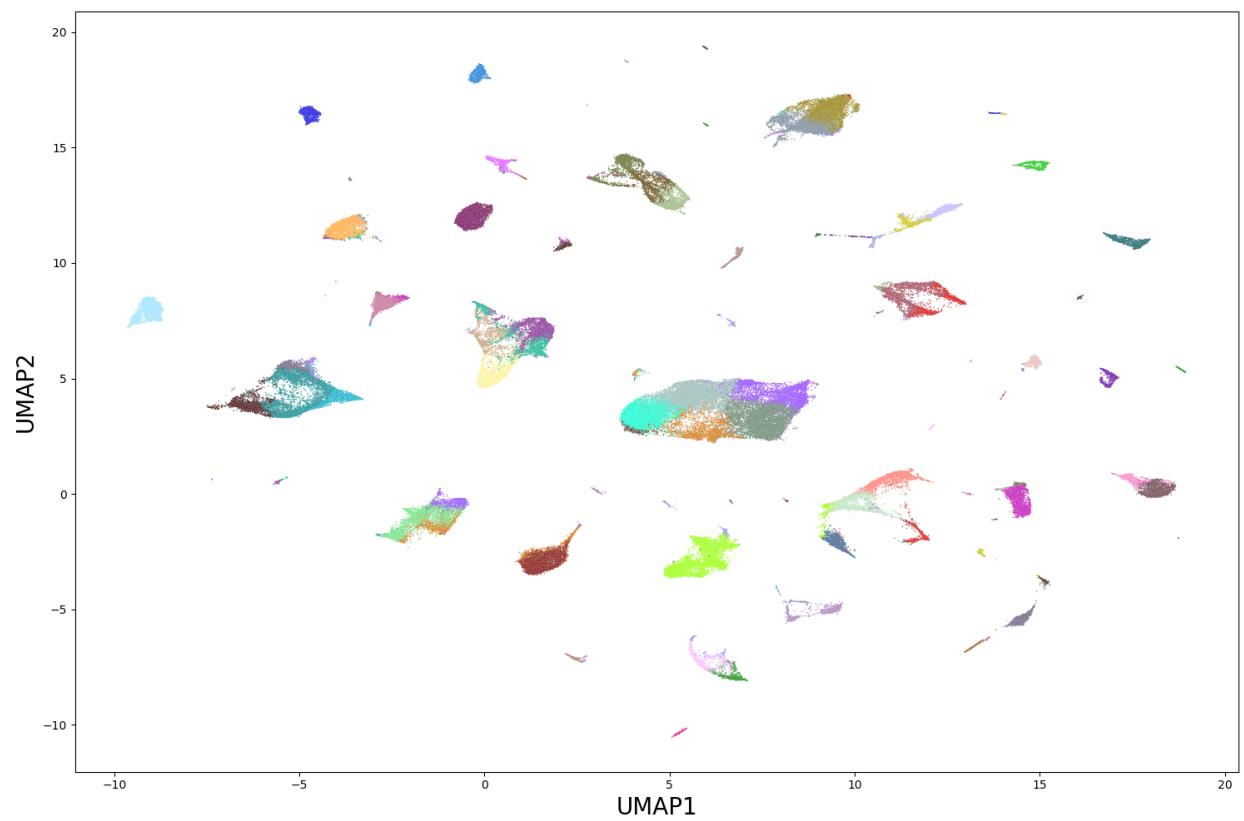


Figure 5: UMAP-kmeans ( $k=50$ )

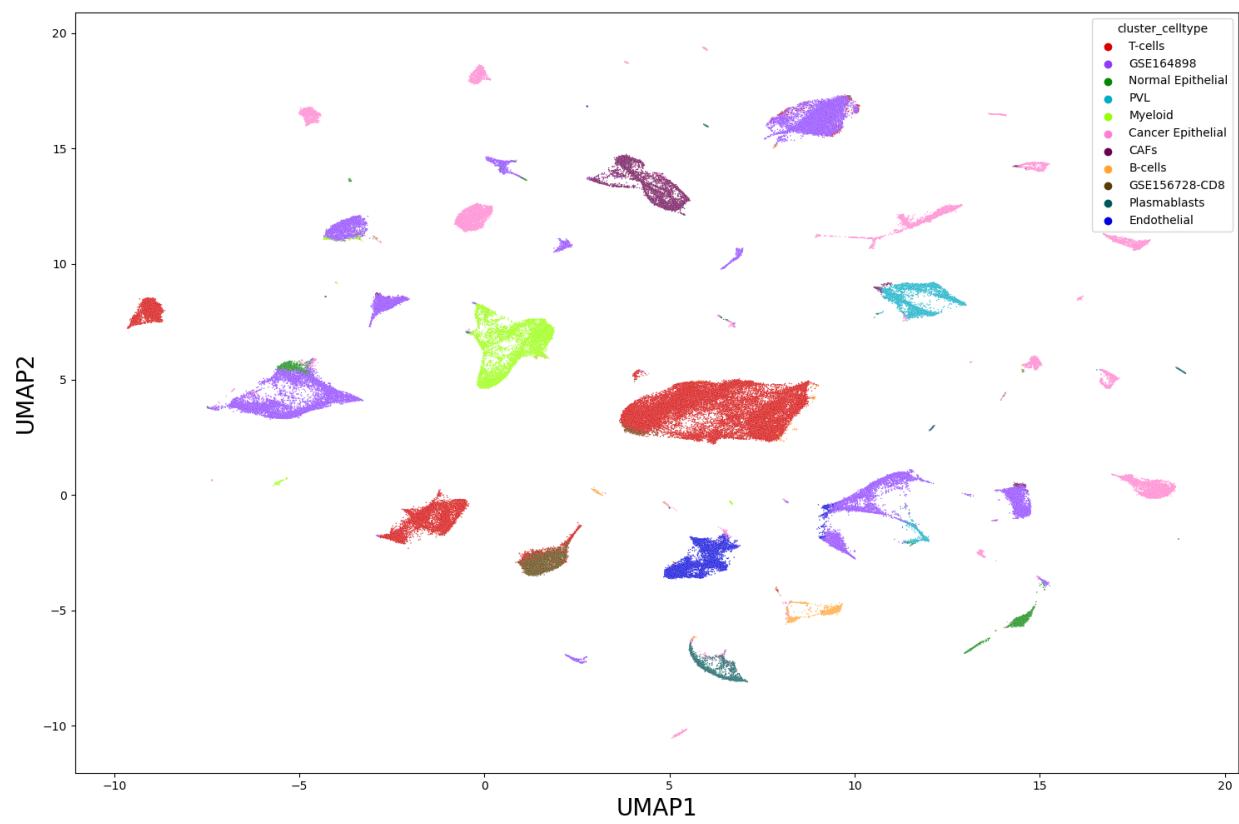


Figure 6: UMAP-kmeans( $k=50$ ) cell-type

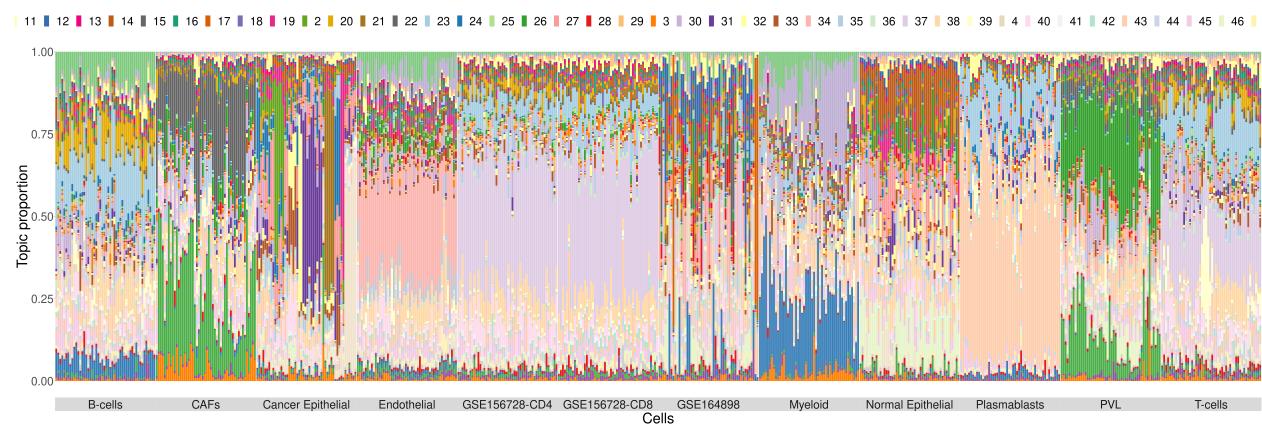


Figure 7: Structure plot cell-type

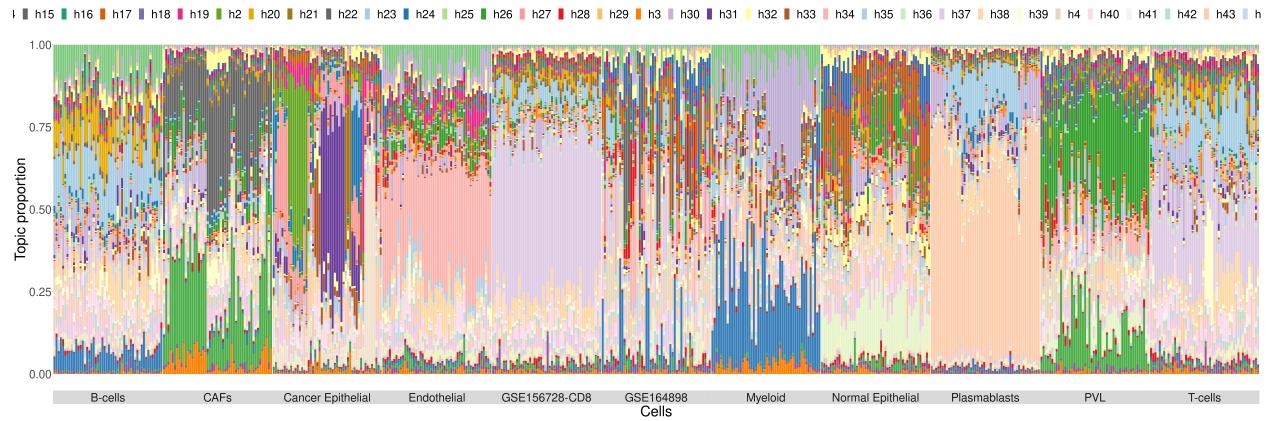


Figure 8: Structure plot kmeans majority cell-type

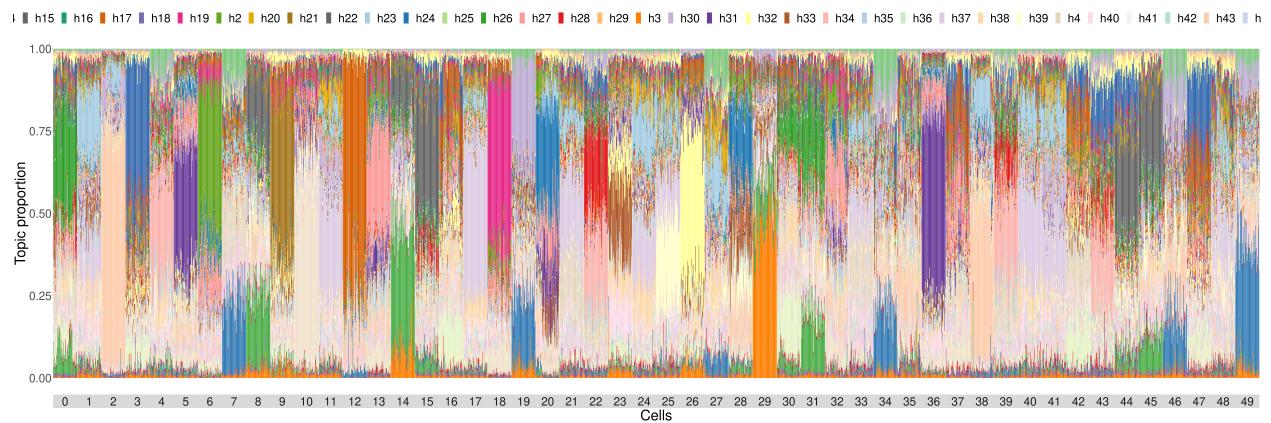


Figure 9: Structure plot kmeans cluster

## Interaction topic analysis

Multinomial-Dirichlet:

$$p(\mathbf{y}_i | \mathbf{q}_i) = \frac{(\sum_g Y_{ig})!}{\prod_g Y_{ig}!} \prod_g q_{ig}^{Y_{ig}}$$

$$\mathbf{q}_i \sim \text{Dir}(\mathbf{q}_i | \rho_i) = \frac{\Gamma(\sum_g \rho_{ig})}{\prod_g \Gamma(\rho_{ig})} \prod_g q_{ig}^{\rho_{ig}-1}$$

Single-cell generative model:

$$p(\mathbf{x}_j | \cdot) = \frac{\Gamma(\sum_g \lambda_{jg})}{\sum_g \Gamma(\lambda_{jg})} \frac{\Gamma(\sum_g \lambda_{jg} + X_{jg})}{\sum_g \Gamma(\lambda_{jg} + X_{jg})}$$

where

$$\lambda_{jg} = \lambda_0 \exp \left( \sum_{t=1}^T \theta_{jt} (\beta_{tg} + \delta_g) \right)$$

$$\lambda_0 = \exp(\tilde{\lambda}_0)$$

$$\sum_t \theta_{jt} = 1$$

Bayesian regularization of the model parameters

$$\beta_{tg} \sim \mathcal{N}(0, 1)$$

Total Expected log-likelihood Lower-bound (ELBO):

$$\begin{aligned}
\frac{J}{n} = & \frac{1}{n} \sum_{i=1}^n \log p(\mathbf{x}_i | \theta_i(\mathbf{z}_i), \beta) \\
& + \frac{1}{n} \sum_{i=1}^n \sum_{t=1}^T D_{\text{KL}}(q(z_{it}) \| p(z_{it})) \\
& + \frac{1}{n} \sum_{t=1}^T \sum_{l=1}^L D_{\text{KL}}(q(\beta_{tl}) \| p(\beta_{tl})) \\
& + \frac{1}{n} \sum_{t=1}^T \sum_{r=1}^R D_{\text{KL}}(q(\beta_{tr}) \| p(\beta_{tr}))
\end{aligned}$$

## Neighbour cells calculation

- removed self neighbour pair
- 18 topics with cell count less than 100 were removed during generating annoy model list.  
Topics were not removed during generating neighbours, only selected topics were used to create a model list.

<b>h35</b>	<b>57</b>
<b>h11</b>	<b>50</b>
<b>h10</b>	<b>39</b>
<b>h8</b>	<b>36</b>
<b>h44</b>	<b>34</b>
<b>h42</b>	<b>20</b>
<b>h29</b>	<b>18</b>
<b>h3</b>	<b>16</b>
<b>h5</b>	<b>13</b>
<b>h16</b>	<b>12</b>
<b>h36</b>	<b>7</b>
<b>h25</b>	<b>6</b>
<b>h47</b>	<b>6</b>
<b>h41</b>	<b>5</b>
<b>h49</b>	<b>4</b>

<b>h15</b>	<b>3</b>
<b>h18</b>	<b>2</b>
<b>h13</b>	<b>2</b>

- Neighbours are calculated from the remaining 32 topics and 5 neighbours from each topic - 159 neighbours for each cell.

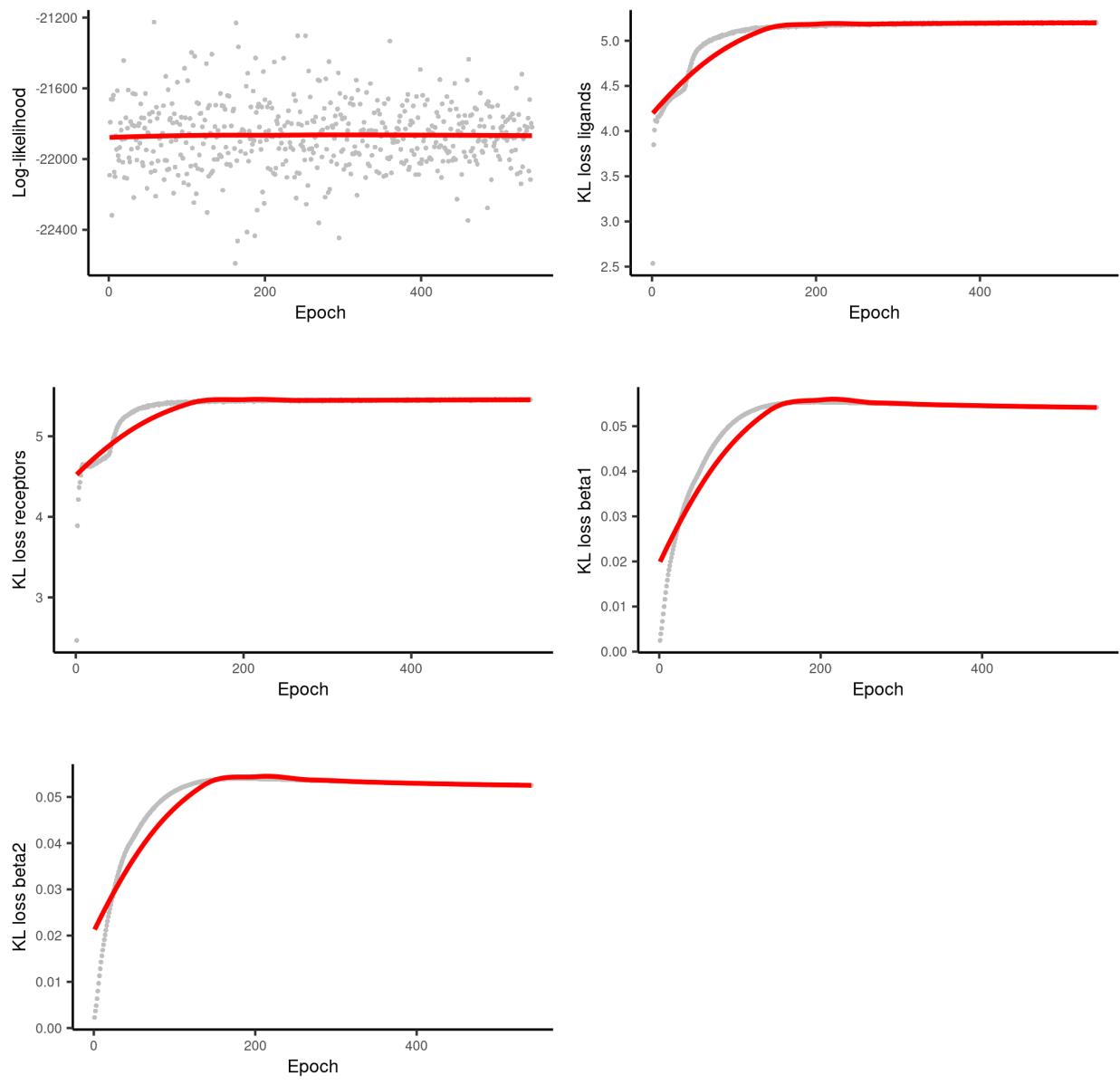


Figure 10: Loss plot

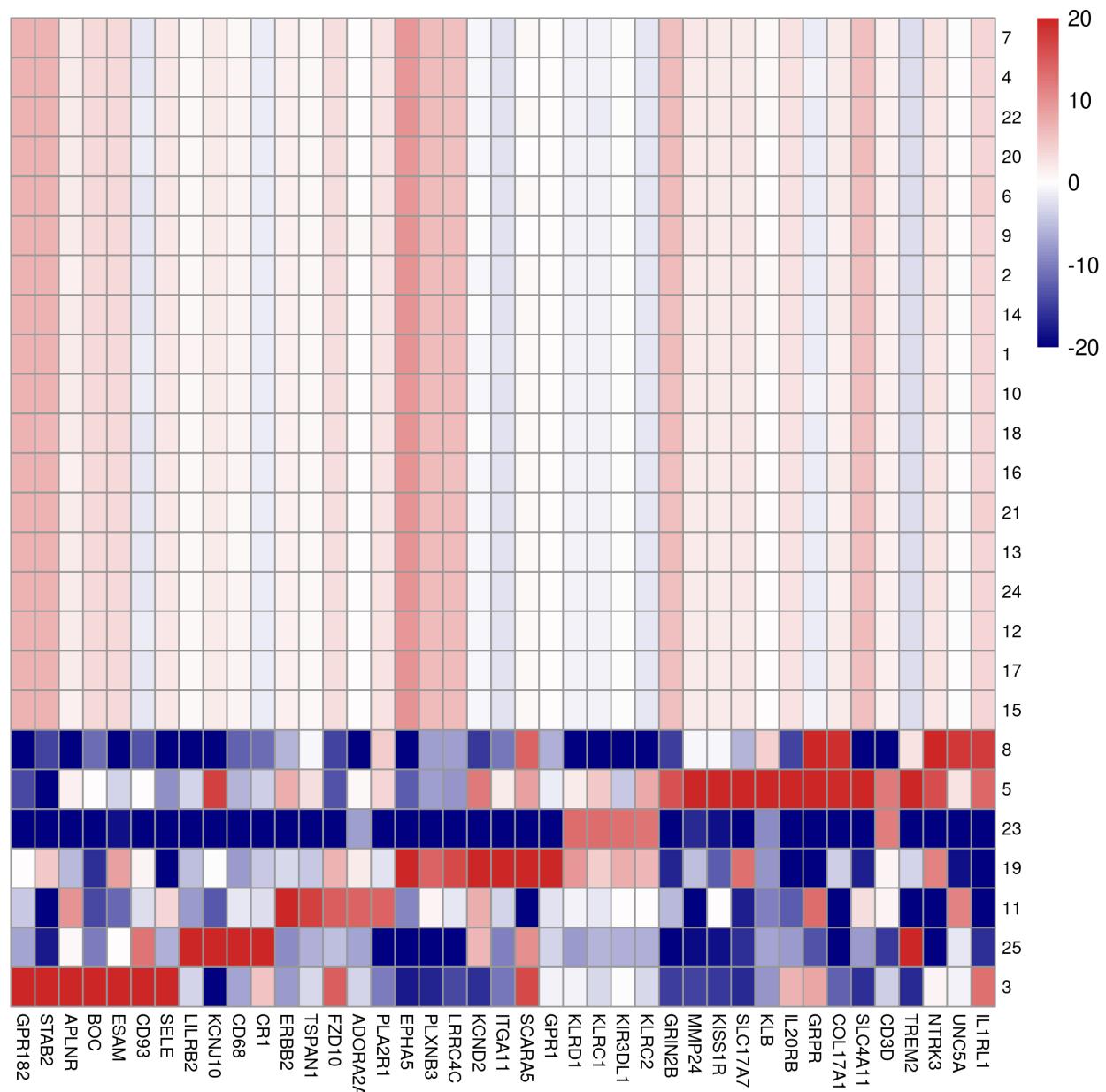


Figure 11: Beta - top receptor genes

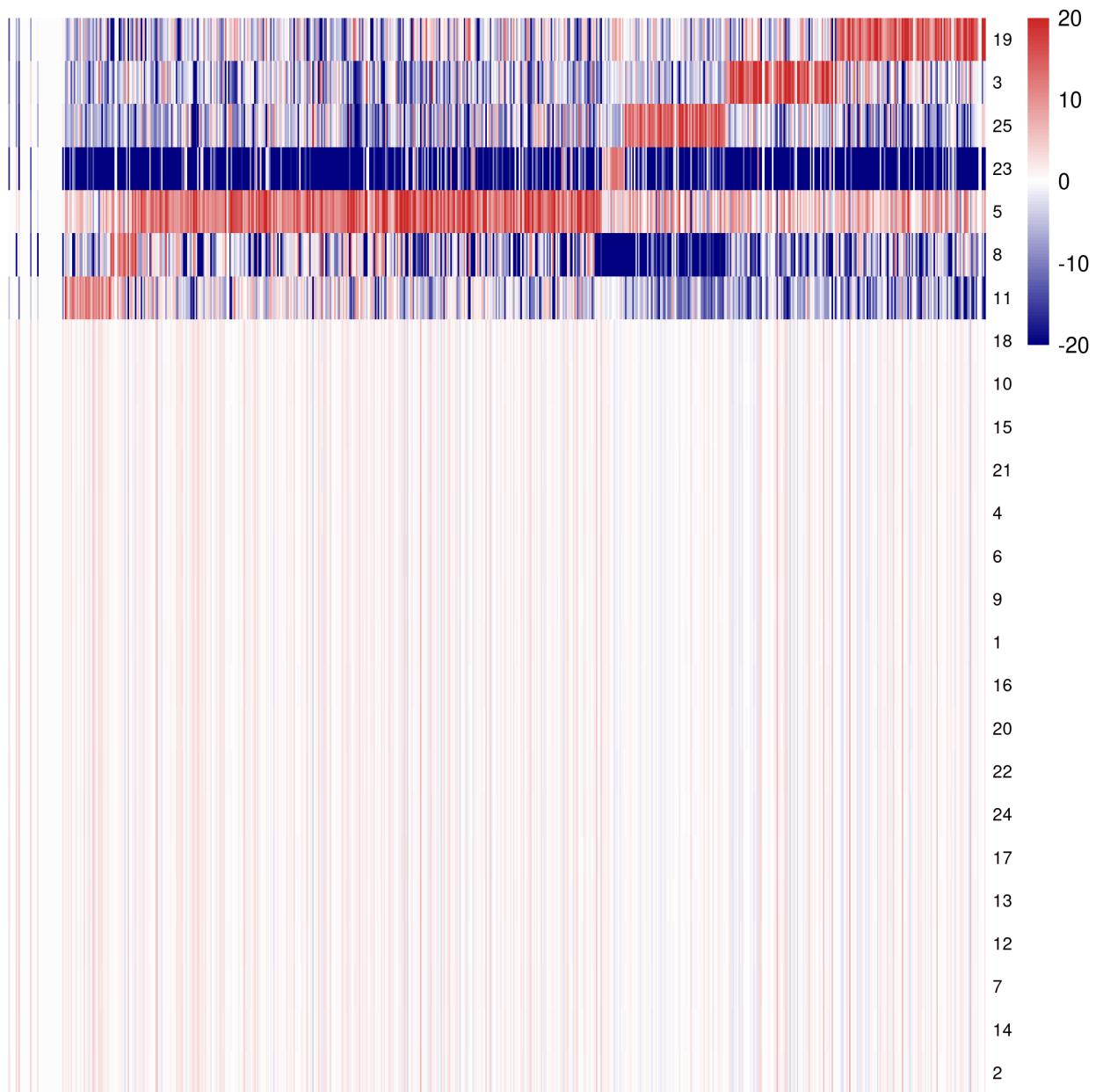


Figure 12: Beta - all receptor genes

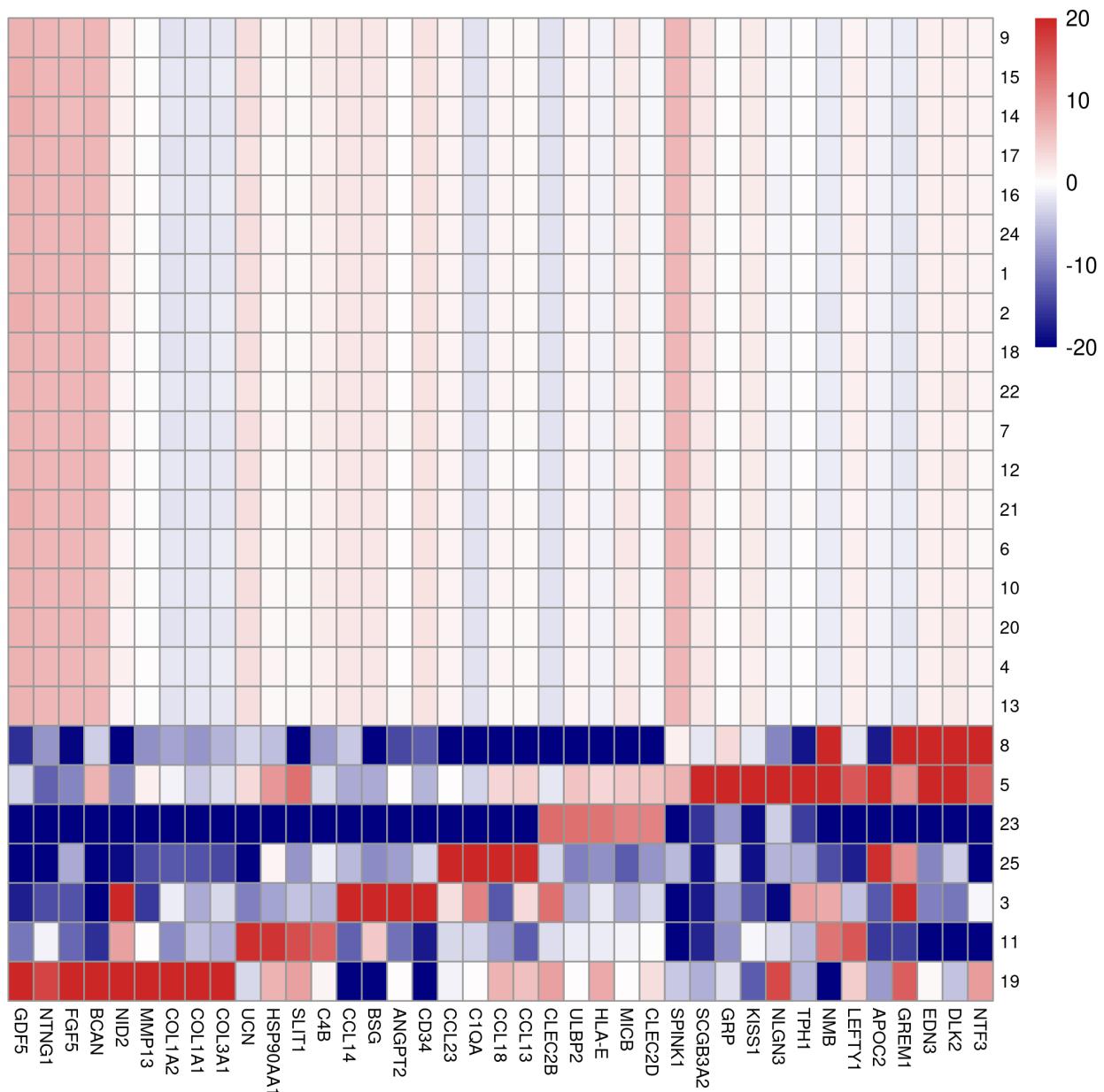


Figure 13: Beta - top ligand genes

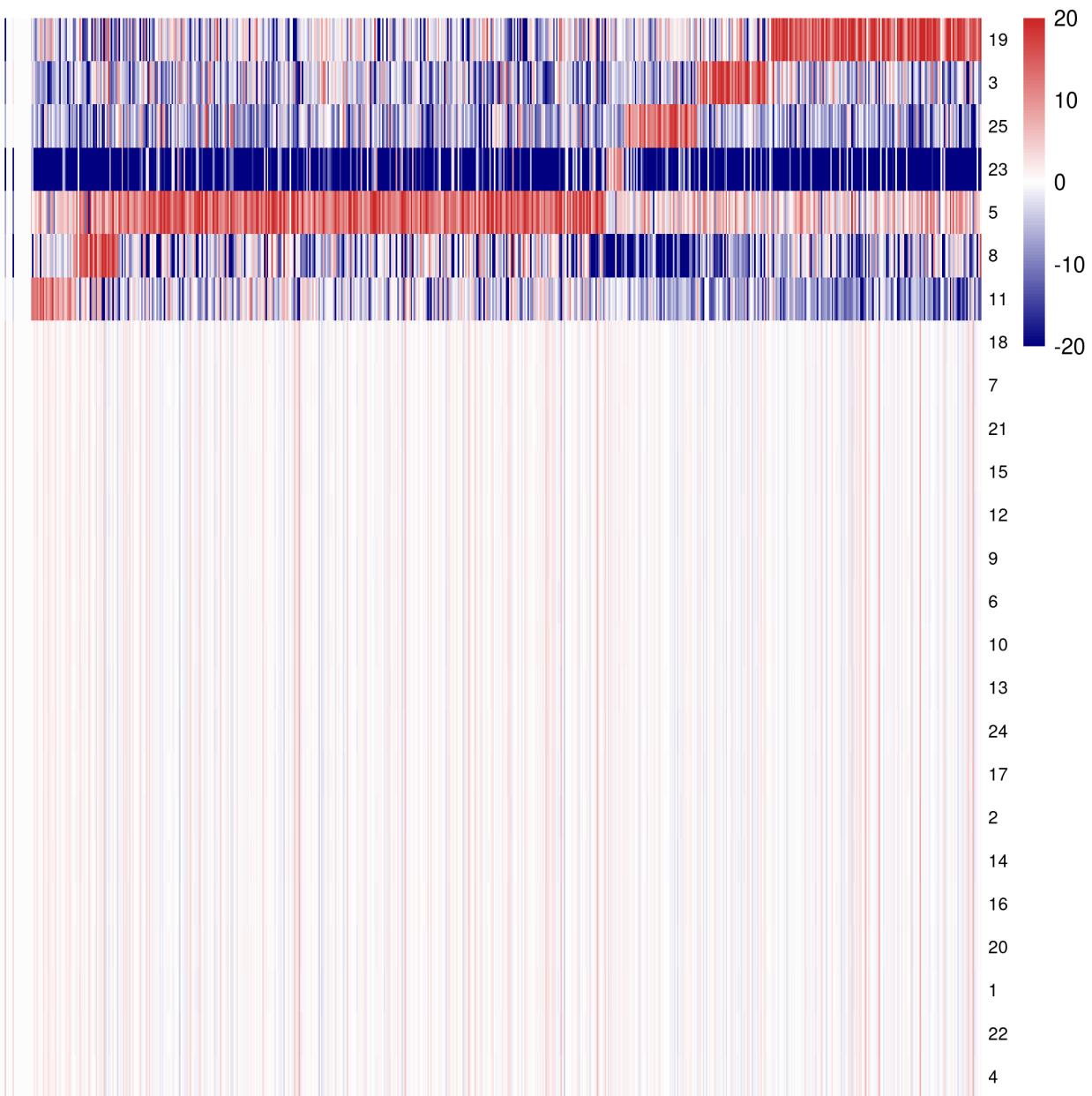


Figure 14: Beta - all ligand genes

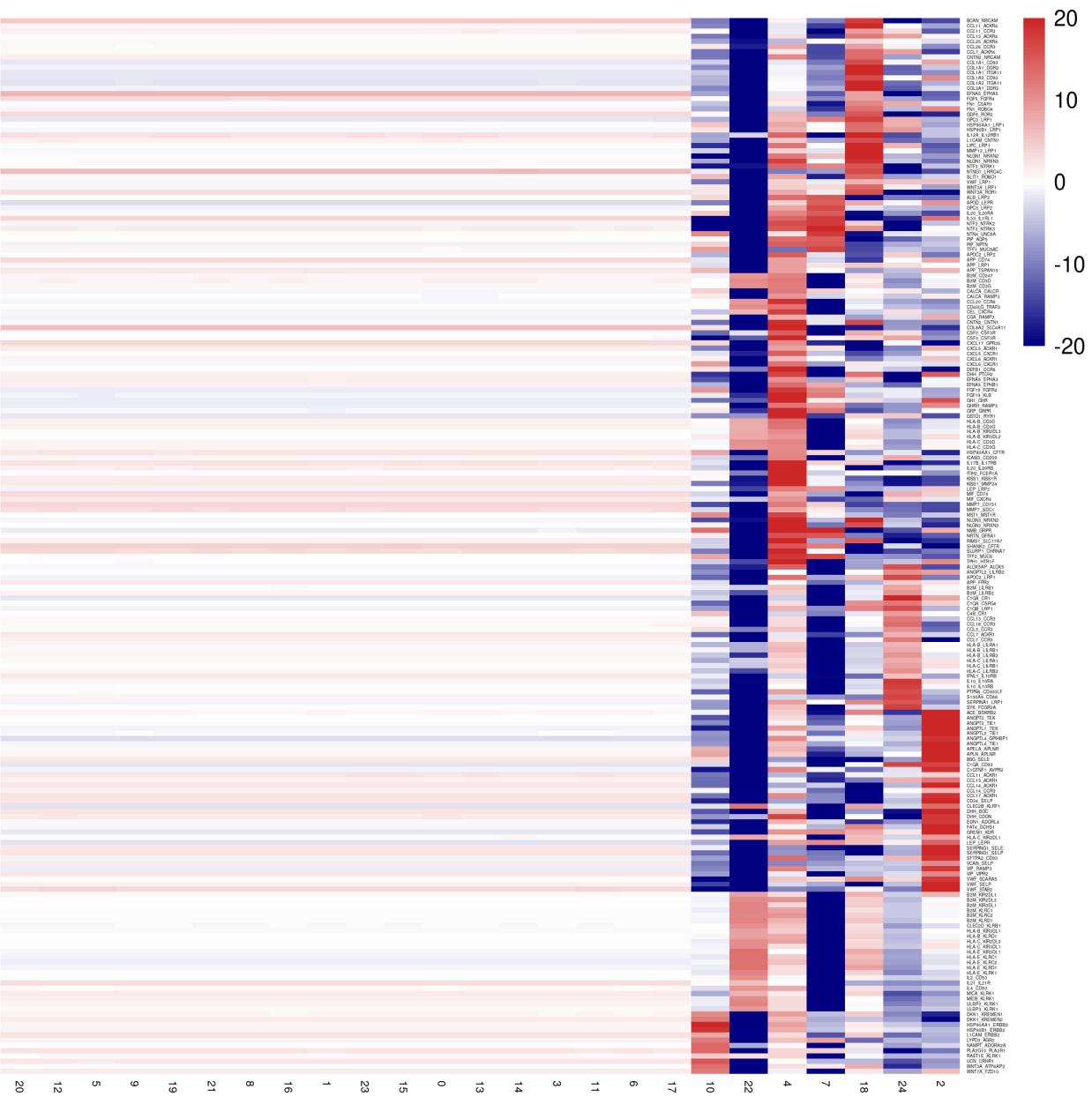


Figure 15: Beta - top lr pair genes