Supplementary Methods

S1. Algorithm for solving the scINSIGHT model

The complete procedure for solving the scINSIGHT model is given in Algorithm 1. It is derived with the following major steps.

In the scINSIGHT model, we minimize the objective function $\mathcal{L}$ by iteratively solving

$$\begin{aligned} V(k,\cdot) \leftarrow \arg\min_{v} \ \mathcal{L}\big(&\{W_{\ell 1}, W_{\ell 2}\}_{\ell=1}^{L}, \{H_j\}_{j=1}^{J}, V(1,\cdot), \ldots, \\ &V(k-1,\cdot), v, V(k+1,\cdot), \ldots, V(K,\cdot)\big) \ , \end{aligned} \tag{s1}$$

for $k = 1, 2, \ldots, K$;

$$\begin{aligned} W_{\ell 2}(\cdot,k) \leftarrow \arg\min_{w} \ \mathcal{L}\big(&\{W_{\ell 1}\}_{\ell=1}^{L}, \{W_{\ell' 2}\}_{\ell'\neq\ell}^{L}, \{H_j\}_{j=1}^{J}, V, W_{\ell 2}(\cdot,1), \\ &\ldots, W_{\ell 2}(\cdot,k-1), w, W_{\ell 2}(\cdot,k+1), \ldots, W_{\ell 2}(\cdot,K)\big) \ , \end{aligned} \tag{s2}$$

for $k = 1, 2, \ldots, K, \ell = 1, 2, \ldots, L$;

$$\begin{aligned} W_{\ell 1}(\cdot,k) \leftarrow \arg\min_{w} \mathcal{L}\big(&\{W_{\ell' 1}\}_{\ell'=1,\ell'\neq\ell}^{L}, \{W_{\ell 2}\}_{\ell=1}^{L}, \{H_j\}_{j=1}^{J}, V, W_{\ell 1}(\cdot,1), \\ &\ldots, W_{\ell 1}(\cdot,k-1), w, W_{\ell 1}(\cdot,k+1), \ldots, W_{\ell 1}(\cdot,k)\big) \end{aligned} \tag{s3}$$

for $k = 1, 2, \ldots, K, \ell = 1, 2, \ldots, L$.

$$\begin{aligned} H_j(k,\cdot) \leftarrow \arg\min_{h} \mathcal{L}\big(&\{W_{\ell 1}, W_{\ell 2}\}_{\ell=1}^{L}, V, \{H'_j\}_{j'=1,j'\neq j}^{J}, H_j(1,\cdot), \ldots, \\ &H_j(k-1,\cdot), h, H_j(k+1,\cdot), \ldots, H_j(K_j,\cdot)\big) \end{aligned} \tag{s4}$$

for $k = 1, 2, \ldots, K_j, j = 1, 2, \ldots, J$.

The minimization problem of (s1)

The minimization problem of $V(k,\cdot)$ can be formulated as

$$\arg\min_{v\geq 0} \sum_{\ell=1}^{L} \frac{1}{m_\ell} \left\| W_{\ell 2}(\cdot,k) v^T - R_{\ell k}^{(V)} \right\|_F^2 ,$$

where

$$R_{\ell k}^{(V)} = X_\ell - W_{\ell 1} H_{j_\ell} - \sum_{k'=1,k'\neq k}^{K} W_{\ell 2}(\cdot,k') V(k',\cdot). \tag{s5}$$

Algorithm 1: The BCD algorithm for the scINSIGHT model

Input : $X_\ell \in \mathbb{R}_+^{m_\ell \times n}, K, K_j, \lambda_1 and \lambda_2$.

Output: $V \in \mathbb{R}_+^{K \times n}, W_{\ell 1} \in \mathbb{R}_+^{m_\ell \times K_{j_\ell}}, W_{\ell 2} \in \mathbb{R}_+^{m_\ell \times K}, H_j \in \mathbb{R}_+^{K_j \times n}$.

Initialize V, $W_{\ell 1}$, $W_{\ell 2}$ and H_j with random nonnegative values.
while *not converged* **do**
  for $k = 1, \ldots, K$ **do**
    $V(k, \cdot) \leftarrow \frac{\left[\sum_{\ell=1}^{L} \frac{1}{m_\ell} \left(R_{\ell k}^{(V)}\right)^T W_{\ell 2}(\cdot, k)\right]_+}{\sum_{\ell=1}^{L} \frac{1}{m_\ell} \|W_{\ell 2}(\cdot, k)\|_2^2}$.
  end
  for $\ell = 1, \ldots, L$ **do**
    for $k = 1, \ldots, K$ **do**
      $W_{\ell 2}(\cdot, k) \leftarrow \left[W_{\ell 2}(\cdot, k) + \frac{\left(X_\ell - W_{\ell 1} H_{j_\ell} - W_{\ell 2} V\right) V^T}{\|V(k, \cdot)\|_2^2}\right]_+$.
      $W_{\ell 1}(\cdot, k) \leftarrow \left[W_{\ell 1}(\cdot, k) + \frac{\left(X_\ell - (1+\lambda_1) W_{\ell 1} H_{j_\ell} - W_{\ell 2} V\right) H_{j_\ell}(k, \cdot)}{(1+\lambda) \left\|H_{j_\ell}(k, \cdot)\right\|_2^2}\right]_+$.
    end
  end
  for $j = 1, \ldots, J$ **do**
    for $k = 1, \ldots, K_j$ **do**
      $H_j(k, \cdot) \leftarrow$
      $\left[H_j(k, \cdot) + \frac{\sum_{j_\ell = j} \frac{1}{m_\ell} (X_\ell - (1+\lambda_1) W_{\ell 1} H_j - W_{\ell 2} V)^T W_{\ell 1}(\cdot, k) - \frac{\lambda_2}{4} \sum_{j' \neq j}^{J} \sum_{k'=1}^{K_{j'}} H_{j'}(k', \cdot)}{\sum_{j_\ell = j} \frac{1+\lambda_1}{m_\ell} \|W_{\ell 1}(\cdot, k)\|_2^2}\right]_+$.
      $\alpha = \|H_j(k, \cdot)\|_2$.
      $H_j(k, \cdot) \leftarrow \frac{H_j(k, \cdot)}{\alpha}$.
      // Adjust all $W_{\ell 1}(\cdot, k)$ satisfying $j_\ell = j$.
      $W_{\ell 1}(\cdot, k) \leftarrow \alpha W_{\ell 1}(\cdot, k)$.
    end
  end
end
for $k = 1, \ldots, K$ **do**
  $\beta = \|V(k, \cdot)\|_2$.
  $V(k, \cdot) \leftarrow \frac{V(k, \cdot)}{\beta}$.
  // Adjust all $W_{\ell 2}(\cdot, k)$.
  $W_{\ell 2}(\cdot, k) \leftarrow \beta W_{\ell 2}(\cdot, k)$.
end

Consider a minimization problem

$$\min_{v\geq 0}\sum_{\ell=1}^{L}\frac{1}{m_\ell}\left\|u_\ell v^T-G_\ell\right\|_F^2,$$

where $G_\ell\in\mathbb{R}^{M_\ell\times N}$ and $u_\ell\in\mathbb{R}^{M_\ell\times 1}$ ($\ell=1,2,\ldots,L$). We further denote $v^T=(v_1,v_2,\ldots,v_N)$ and $G_\ell=[g_{\ell 1},g_{\ell 2},\ldots,g_{\ell N}]$. Since $v\geq 0$, we have

$$\min_{v\geq 0}\sum_{\ell=1}^{L}\frac{1}{m_\ell}\left\|u_\ell v^T-G_\ell\right\|_F^2=\sum_{n=1}^{N}\min_{v_n\geq 0}\sum_{\ell=1}^{L}\frac{1}{m_\ell}\left\|u_\ell v_n-g_{\ell n}\right\|_2^2,$$

where the minimum is achieved at

$$v_n=\max\left\{0,\frac{\sum_{\ell=1}^{L}\frac{1}{m_\ell}u_\ell^T g_{\ell n}}{\sum_{\ell=1}^{L}\frac{1}{m_\ell}\left\|u_\ell\right\|_2^2}\right\}=\frac{\left[\sum_{\ell=1}^{L}\frac{1}{m_\ell}u_\ell^T g_{\ell n}\right]_+}{\sum_{\ell=1}^{L}\frac{1}{m_\ell}\left\|u_\ell\right\|_2^2}.$$

Therefore, the solution of (s1) is

$$V(k,\cdot)\leftarrow\frac{\left[\sum_{\ell=1}^{L}\frac{1}{m_\ell}\left(R_{\ell k}^{(V)}\right)^T W_{\ell 2}(\cdot,k)\right]_+}{\sum_{\ell=1}^{L}\frac{1}{m_\ell}\left\|W_{\ell 2}(\cdot,k)\right\|_2^2}. \tag{s6}$$

Replacing $R_{\ell k}^{(V)}$ in (s6) with expression in (s5), we have

$$V(k,\cdot)\leftarrow\left[V(k,\cdot)+\frac{\sum_{\ell=1}^{L}\frac{1}{m_\ell}\left(X_\ell-W_{\ell 1}H_{j_\ell}-W_{\ell 2}V\right)^T W_{\ell 2}(\cdot,k)}{\sum_{\ell=1}^{L}\frac{1}{m_\ell}\left\|W_{\ell 2}(\cdot,k)\right\|_2^2}\right]_+.$$

The minimization problem and solution of (s2)

The minimization problem of $W_{\ell 2}(\cdot,k)$ appears as

$$\min_{w\geq 0}\frac{1}{m_\ell}\left\|V(k,\cdot)w^T-\left(R_{\ell k}^{V}\right)^T\right\|_F^2.$$

Using a similar approach as above, the solution of (s2) is

$$W_{\ell 2}(\cdot,k)\leftarrow\frac{\left[R_{\ell k}^{(V)}V(k,\cdot)\right]_+}{\left\|V(k,\cdot)\right\|_2^2}. \tag{s7}$$

Replacing $R_{\ell k}^{(V)}$ in (s7) with expression in (s5), we have

$$W_{\ell 2}(\cdot,k)\leftarrow\left[W_{\ell 2}(\cdot,k)+\frac{\left(X_\ell-W_{\ell 1}H_{j_\ell}-W_{\ell 2}V\right)V^T}{\left\|V(k,\cdot)\right\|_2^2}\right]_+.$$

The minimization problem and solution of (s3)

The minimization problem of $W_{\ell 1}(k,\cdot)$ appears as

$$\min_{w\geq 0}\frac{1}{m_\ell}\left\|H_{j_\ell}(k,\cdot)w^T-\left(R_{\ell k}^{(H)}\right)^T\right\|_F^2+\frac{\lambda}{m_\ell}\left\|H_{j_\ell}(k,\cdot)w^T+S_{\ell k}^T\right\|_F^2$$

where

$$S_{\ell k}=\sum_{k'=1,k'\neq k}^{K_{j_\ell}}W_{\ell 1}(\cdot,k')H_{j_\ell}(k',\cdot)^T, \tag{s8}$$

$$R_{\ell k}^{(H)}=X_\ell-W_{\ell 2}V-S_{\ell k}. \tag{s9}$$

Using a similar approach as above, the solution of (s3) is

$$W_{\ell 1}(\cdot,k)\leftarrow\frac{\left[\left(R_{\ell k}^{(H)}-\lambda S_{\ell k}\right)H_{j_\ell}(k,\cdot)\right]_+}{(1+\lambda)\left\|H_{j_\ell}(k,\cdot)\right\|_2^2}. \tag{s10}$$

Replacing $S_{\ell k}$ and $R_{\ell k}^{(H)}$ in (s10) with expression in (s8) and (s9), the solution can be rewritten as

$$W_{\ell 1}(\cdot,k)\leftarrow\left[W_{\ell 1}(\cdot,k)+\frac{\left(X_\ell-(1+\lambda)W_{\ell 1}H_{j_\ell}-W_{\ell 2}V\right)H_{j_\ell}(k,\cdot)}{(1+\lambda)\left\|H_{j_\ell}(k,\cdot)\right\|_2^2}\right]_+.$$

The minimization problem and solution of (s4)

The minimization problem of $H_j(k,\cdot)$ appears as

$$\min_{h\geq 0}\sum_{j_\ell=j}\frac{1}{m_\ell}\left[\left\|W_{\ell 1}(\cdot,k)h^T-R_{\ell k}^{(H)}\right\|+\lambda_1\left\|W_{\ell 1}(\cdot,k)h^T+S_{\ell k}\right\|_F^2\right]+\frac{\lambda_2}{2}h^T\sum_{j'=1,j'\neq j}^{J}\sum_{k'=1}^{K_{j'}}H_{j'}(k',\cdot).$$

Consider a minimization problem

$$\min_{v\geq 0}\sum_{i\in I}\frac{1}{m_i}\left[\left\|u_iv^T-G_i\right\|_F^2+\lambda_1\left\|u_iv^T+Q_i\right\|_F^2\right]+\lambda_2v^Tw,$$

where $G_i,Q_i\in\mathbb{R}^{M_i\times N},u_i\in\mathbb{R}^{m_i\times 1},i\in I$ and $H_j\in\mathbb{R}^{K_j\times N}$ are given. Let $v^T=(v_1,2,\ldots,v_N),G_i=[g_{i,1},\ldots,g_{i,N}],Q_i=[q_{i,1},\ldots,q_{i,N}]$ and $H_j=[h_{j,1},\ldots,h_{j,N}]$. Since $v\geq 0$, we have

$$\begin{aligned}&\min_{v\geq 0}\sum_{i\in I}\frac{1}{m_i}\left[\left\|u_iv^T-G_i\right\|_F^2+\lambda_1\left\|u_iv^T+Q_i\right\|_F^2\right]+\lambda_2v^Tw\\&=\sum_{n=1}^{N}\min_{v_n\geq 0}\sum_{i\in I}\frac{1}{m_i}\left[\left\|u_iv_n-g_{i,n}\right\|_2^2+\lambda_1\left\|u_iv_n+q_{i,n}\right\|_2^2\right]+\lambda_2v_nw_n.\end{aligned}$$

Solving the above problem, that the solution of (s4) can be obtained:

$$H_j(k,\cdot) \leftarrow \left[H_j(k,\cdot) + \frac{\sum_{j_\ell=j} \frac{1}{m_\ell} \left(R_{\ell k}^{(H)} - \lambda_1 S_{\ell k} \right)^T W_{\ell 1}(\cdot,k) - \frac{\lambda_2}{4} \sum_{j'=1,j'\neq j}^{J} \sum_{k'=1}^{K_{j'}} H_{j'}(k',\cdot)}{\sum_{j_\ell=j} \frac{1+\lambda_1}{m_\ell} \left\| W_{\ell 1}(\cdot,k) \right\|_2^2} \right]_+ . \tag{s11}$$

Replacing $S_{\ell k}$ and $R_{\ell k}^{(H)}$ in (s11) with expression in (s8) and (s9) we have

$$H_j(k,\cdot) \leftarrow \left[H_j(k,\cdot) + \frac{\sum_{j_\ell=j} \frac{1}{m_\ell} \left(X_\ell - (1+\lambda_1) W_{\ell 1} H_j - W_{\ell 2} V \right)^T W_{\ell 1}(\cdot,k) - \frac{\lambda_2}{4} \sum_{j'=1,j'\neq j}^{J} \sum_{k'=1}^{K_{j'}} H_{j'}(k',\cdot)}{\sum_{j_\ell=j} \frac{1+\lambda_1}{m_\ell} \left\| W_{\ell 1}(\cdot,k) \right\|_2^2} \right]_+ .$$

After we update $H_j(k,\cdot)$, we need to calculate the $L2$ norm of $H_j(k,\cdot)$ as $\alpha = \|H_j(k,\cdot)\|_2$, then normalize it by

$$H_j(k,\cdot) \leftarrow \frac{H_j(k,\cdot)}{\alpha} ,$$

and adjust all $W_{\ell 1}(\cdot,k)$ satisfying $j_\ell = j$ by

$$W_{j_\ell}(\cdot,k) \leftarrow \alpha W_{j_\ell}(\cdot,k) .$$

After we finish the iteration, we need to calculate the $L2$ norm of $V(k,\cdot)$ as $\beta = \|V(k,\cdot)\|_2$, then normalize it by

$$V(k,\cdot) \leftarrow \frac{V(k,\cdot)}{\beta} ,$$

and adjust all $W_{\ell 2}(\cdot,k)$ by

$$W_{\ell 2}(\cdot,k) \leftarrow \beta W_{\ell 2}(\cdot,k) ,$$

for $\ell = 1,2,\ldots,L, k = 1,2,\ldots,K$.