

# GPNSF: A model using GP priors and NMF to facilitate multi-omics data integration

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January 6, 2026

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# 1 Related Work

Jin et al. [1] proposed joint matrix factorization method to integrate multi omics data. The model aims to address two major challenges simultaneously: (i) the extremely sparse and near-binary nature of single-cell epigenomic data and (ii) the integration of this binary epigenomic data with the scRNA-seq data, which are often continuous after being normalized.

$$\begin{aligned} & \min_{W_1, W_2, H, Z \geq 0} \alpha \|X_1 - W_1 H\|_F^2 \\ & + \|X_2(Z \circ R) - W_2 H\|_F^2 + \lambda \|Z - H^T H\|_F^2 \\ & + \gamma \sum_j \|H_{\cdot j}\|_1^2, \end{aligned}$$

Figure 1: scAI Loss Function

A method considers the spatial information of single-cell data by using Gaussian process [3], but it's applied to single omic data (spatial count data).

$$y_{ij} \sim \text{Poi}(v_i \lambda_{ij})$$

$$\lambda_{ij} = \sum_{l=1}^L w_{jl} e^{f_{il}}$$

$$f_{il} = f_l(\mathbf{x}_i) \sim \text{GP}(\mu_l(\mathbf{x}_i), k_l(\mathbf{x}_i, X)).$$

Figure 2: NSF

## 2 Model

### 2.1 Model Overview

We have two data matrices  $X_1 = (x_{ij}^{(1)}) \in \mathbb{R}_+^{n \times p}$  and  $X_2 = (x_{ij}^{(2)}) \in \mathbb{R}_+^{n \times q}$  with the same number of samples  $n$  (they are samples from the same cells), but different numbers of features  $p$  and  $q$ . We assume that both matrices can be approximated by a low-dimensional representation  $H \in \mathbb{R}^{n \times K}$  and factor loading matrices  $W_1 = (w_{ij}^{(1)}) \in \mathbb{R}_+^{K \times p}$  and  $W_2 = (w_{ij}^{(2)}) \in \mathbb{R}_+^{K \times q}$ .

Let the spatial 2-D coordinates of the  $i$ -th sample in the low-dimensional space be denoted as  $\mathbf{s}_i = (s_{i1}, s_{i2})$ . The approximation we suppose is different from the standard NMF in three aspects:

- (1)  $H$  is no longer a matrix of numbers, but a matrix of distributions priored by the spatial coordinates of the samples, i.e.,

$$h_{ik} = h_k(\mathbf{s}_i) = \mathcal{GP}(\mu_k(\mathbf{s}_i), K_k(\mathbf{s}_i, \mathbf{S})) \quad (1)$$

$$\mu_k(\mathbf{s}_i) = \beta_{0k} + \mathbf{s}_i^\top \boldsymbol{\beta}_{1k}, \quad i = 1, \dots, n, \quad k = 1, \dots, K \quad (2)$$

$$K_k(\mathbf{s}_i, \mathbf{S}) = \gamma_1 \mathbf{1}_{\{i=j\}} + \gamma_2 \exp\left(-\frac{\|\mathbf{s}_i - \mathbf{s}_j\|}{2l}\right) \quad (3)$$

We sample from these  $K$  multi-variated Gaussians to get  $H$  each time.

- (2) While  $W$  is restricted to non-negative,  $H$  is not because it is sampled from

some Gaussians. To compromise this, we calculate:

$$y_{ij}^{(r)} = \sum_{k=1}^K \exp(h_{ik}) w_{kj}^{(r)}, \quad r = 1, 2 \quad (4)$$

- (3)  $X$  is generated by under likelihood assumptions, if  $X_1$  is scRNA-seq data,  $X_2$  is ATAC data, then:

$$x_{ij}^{(1)} | y_{ij}^{(1)} \sim NB(y_{ij}^{(1)}, \theta_j) \quad (5)$$

$$x_{ij}^{(2)} | y_{ij}^{(2)} \sim Bernoulli(y_{ij}^{(2)} \lambda_j) \quad (6)$$

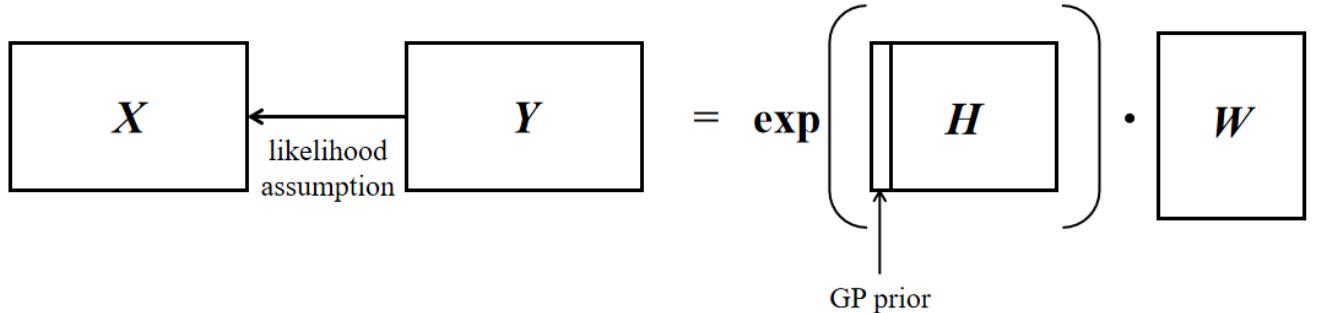


Figure 3: Model Skeleton

## 2.2 Variants

- Data enhancing step for scATAC data can be added to the model if we define  $Z = (\mu_1(S), \dots, \mu_K(S))^\top (\mu_1(S), \dots, \mu_K(S))$  as the cell-to-cell similarity matrix.

- Non-spatial latent features can be added to the model if we separate the rows of  $H$  to two parts: one has GP prior and another has standard Gaussian prior.

## 3 Optimization

### 3.1 Inducing Point Locations

We assume a set of inducing point locations  $\mathbf{z}_m$  indexed by  $m = 1, \dots, M$ . If  $M = n$  we set  $\mathbf{z}_m$  to be the spatial coordinates  $S$ . Otherwise, for  $M < N$  we set  $\mathbf{z}_m$  to be the center points of a k-means clustering (with  $k = M$ ) applied to  $S$ . Let

$$u_{mk} = \mathcal{GP}(\mu_k(\mathbf{z}_m), K_k(\mathbf{z}_m, Z)) \quad (7)$$

be the inducing points, i.e., the Gaussian process evaluation of the inducing locations.

The prior of the inducing points followed by 7 is

$$p(U; Z) = \prod_{k=1}^K p(u_k; Z) \quad (8)$$

$$p(u_k; Z) = \mathcal{N}(\mu_k(Z), K_{uuk}) \quad (9)$$

$$[K_{uuk}]_{m,m'} = K_k(\mathbf{z}_m, \mathbf{z}'_{m'}) \quad (10)$$

Since  $H$  and  $U$  are jointly normal-distributed, the conditional probability of  $H$

can be calculated given  $U$ :

$$p(H|U; S, Z) = \prod_{k=1}^K p(h_k|u_k; S, Z) \quad (11)$$

$$p(h_k|u_k; S, Z) = \mathcal{N}(\mu_{h|u,k}, K_{h|u,k}) \quad (12)$$

$$\mu_{h|u,k} = \mu_k(S) + K_{uhk}^\top K_{uuk}^{-1} (u_k - \mu_k(Z)) \quad (13)$$

$$K_{h|u,k} = K_{hhk} - K_{uhk}^\top K_{uuk}^{-1} K_{uhk} \quad (14)$$

$$[K_{uhk}]_{m,i} = K_k(z_m, x_i) \quad (15)$$

## 3.2 Variational Inference

We use the following approximation to facilitate variational inference:

$$q(U, H; S, Z) = p(H|U; S, Z)q(U; Z) \quad (16)$$

where  $q(U; Z)$  is a parameterized Gaussian:

$$q(U; Z) = \prod_{k=1}^K q(u_k; Z) = \prod_{k=1}^K \mathcal{N}(\delta_k, \Omega_k) \quad (17)$$

We need to draw samples from the distribution of  $H$  under the variational ap-

proximation, which means we need to marginalize  $U$  in  $q(U, H; S, Z)$  [2]:

$$q(H; S, Z) = \prod_{k=1}^K q(h_k | \delta_k, \Omega_k; S, Z) \quad (18)$$

$$q(h_k | \delta_k, \Omega_k; S, Z) = \int_{u_k} q(u_k, h_k; S, Z) = \mathcal{N}(\tilde{\mu}_k, \tilde{\Sigma}_k) \quad (19)$$

$$\tilde{\mu}_k = \mu_k(S) + K_{uhk}^\top K_{uuk}^{-1} (\delta_k - \mu_k(Z)) \quad (20)$$

$$\tilde{\Sigma}_k = K_{hhk} - K_{uhk}^\top K_{uuk}^{-1} (K_{uuk} - \Omega_k) K_{uuk}^{-1} K_{uhk} \quad (21)$$

Next, we find ELBO as the loss function [2]. Note that we ignore the subscript of  $X_1$  and  $X_2$  and drop the notations of  $S$  and  $Z$ :

$$\log p(X) = \mathbb{E}_{q(U, H)} [\log p(X)] \quad (22)$$

$$= \mathbb{E}_{q(U, H)} \left[ \log \frac{p(X|H)p(H|U)p(U)}{p(U, H)} \right] \quad (23)$$

$$= \mathbb{E}_{q(U, H)} \left[ \log \frac{p(X|H)p(H|U)p(U)}{p(U, H)} \cdot \frac{q(H, U)}{q(H, U)} \right] \quad (24)$$

$$= \mathbb{E}_{q(U, H)} \left[ \log \frac{p(X|H)p(H|U)p(U)}{p(H|U)q(U)} \cdot \frac{q(H, U)}{p(H, U)} \right] \quad (25)$$

$$= \underbrace{\mathbb{E}_{q(U, H)} [\log p(X|H)] - \sum_{k=1}^K \text{KL}(q(u_k) || p(u_k))}_{\text{ELBO}} + \text{KL}(q(H, U) || p(H, U)) \quad (26)$$

### 3.3 Loss Function

The loss function for whole model should both consider the reconstruction loss of  $X_1$  and  $X_2$ :

$$\mathcal{L} \triangleq \mathbb{E}_{q(U,H)} [\log p(X_1|H)] + \mathbb{E}_{q(U,H)} [\log p(X_2|H)] - \eta \sum_{k=1}^K \text{KL}(q(u_k) || p(u_k)) \quad (27)$$

where  $\eta$  is a hyperparameter to determine the proportion of reconstruction term and KL term.

The KL term in ELBO has a closed form since  $q(u_k)$  and  $p(u_k)$  are both Gaussians:

$$\begin{aligned} \text{KL}(q(u_k) || p(u_k)) &= \\ \frac{1}{2} \left[ \log \frac{|K_{uuk}|}{|\Omega_k|} - M + \text{tr}(K_{uuk}^{-1} \Omega_k) + (\delta_k - \mu_k(Z))^\top K_{uuk} (\delta_k - \mu_k(Z)) \right] \end{aligned} \quad (28)$$

The expected log likelihood in ELBO takes more effect to compute.

$$\mathbb{E}_{q(U,H)} [\log p(X|H)] = \sum_{i=1}^n \sum_{j=1}^p \mathbb{E}_{q(U,H)} \left[ \zeta \left( x_{ij} | \nu_j \sum_{k=1}^K \exp(h_{ik}) w_{kj} \right) \right] \quad (29)$$

$$= \sum_{i=1}^n \sum_{j=1}^p \mathbb{E}_{q(H)} \left[ \zeta \left( x_{ij} | \nu_j \sum_{k=1}^K \exp(h_{ik}) w_{kj} \right) \right] \quad (30)$$

$$= \sum_{i=1}^n \sum_{j=1}^p \mathbb{E}_{q(h_{i1}, \dots, h_{iK})} \left[ \zeta \left( x_{ij} | \nu_j \sum_{k=1}^K \exp(h_{ik}) w_{kj} \right) \right] \quad (31)$$

Note that  $h_{i1}, \dots, h_{iK}$  are independent if  $i$  is fixed, so we can compute  $q(h_{i,:})$  by:

$$q(h_{i,:}) = \prod_{k=1}^K q(h_{ik}) = \prod_{k=1}^K \mathcal{N}([\tilde{\mu}_k]_i, [\tilde{\Sigma}_k]_{i,i}) \quad (32)$$

$$[\tilde{\mu}_k]_i = \mu_k(\mathbf{s}_i) + \alpha_k(\mathbf{s}_i)^\top (\delta_k - \mu_k(Z)) \quad (33)$$

$$[\tilde{\Sigma}_k]_{i,i} = K_k(\mathbf{s}_i, \mathbf{s}_i) - \alpha_k(\mathbf{s}_i)^\top (K_{uuk} - \Omega_k) \alpha_k(\mathbf{s}_i) \quad (34)$$

$$\text{where } \alpha_k(\mathbf{s}_i) \triangleq K_{uuk}^{-1} [K_{uhk}]_{:,i} \quad (35)$$

So, instead of sampling  $H$  following equation 18, we actually sample  $H$  row by row following equation 32. Finally, the expectation is estimated by Monte Carlo procedure, i.e., we draw  $s$  samples from the distribution of  $H$  and calculate the mean of  $s$  log likelihoods.

## References

- [1] Suoqin Jin, Lihua Zhang, and Qing Nie. scai: an unsupervised approach for the integrative analysis of parallel single-cell transcriptomic and epigenomic profiles. *Genome biology*, 21(1):25, 2020.
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- [3] F William Townes and Barbara E Engelhardt. Nonnegative spatial factorization applied to spatial genomics. *Nature methods*, 20(2):229–238, 2023.