1 Cell type classification using a VAE-based framework

Here we consider the gene counts vector x for each cell in a single cell RNA-seq data as a sample from a zero-inflated negative bionomial (ZINB) distribution. The parameters of the ZINB distribution are determined from two random variables, a latent cell state $z_1 \sim N(\mu_{z1}, \sigma_{z1}^2)$ and the library size $l \sim LogNorm(\mu_l, \sigma_l)$. Furthermore, μ_{z1} and σ_{z1} are determined by both cell type $y \sim Categorical(\pi_y)$ and a basal cell state $z_2 \sim N(\mu_{z2}, \sigma_{z2}^2)$ that captures non-cell-type information such as cell cycle.

With these assumptions, we can factorize the joint probability of x and latent variables as $p(x, z_1, z_2, l, y) = p(x|z_1, l)p(z_1|z_2, y)p(y)p(l)p(z_2)$

Further more, we consider the following variational factorization of the posterior distribution $q(z_1, z_2, l, y|x) = q(z_2|z_1, y)q(y|z_1)q(l|x)q(z_1|x)$. This posterior distribution is approximated by neural networks through a VAE framework.

The ELBO loss of the VAE can be derived as follows:

Let H = {z1, z2, l, y}

$$\log P(x) = \log \int_H p(x, H)dH \tag{1}$$

$$= \log E_{q(H)}[\frac{p(x, H)}{q(H)}] \tag{2}$$

$$\geq E_{q(H)} \log \frac{p(x, H)}{q(H)} \tag{3}$$

$$= E_{q(z_1, z_2, l, y)} \log \frac{p(x|z_1, l)p(z_1|z_2, y)p(y)p(l)p(z_2)}{q(z_2|z_1, y)q(y|z_1)q(l|x)q(z_1|x)} \tag{4}$$

$$= E_{q(z_1|x)q(l|x))} \log p(x|z_1, l) + E_{q(z_1, z_2, y|x)} \log \frac{p(z_1|z_2, y)}{q(z_1|x)} \tag{5}$$

$$+ E_{q(z_1, y|x)} \log \frac{p(y)}{q(y|z_1)} + E_{q(l|x)} \log \frac{p(l)}{q(l|x)} \tag{6}$$

$$+ E_{q(z_1, z_2, y|x)} \log \frac{p(z_2)}{q(z_2|z_1, y)} \tag{7}$$

where

$$E_{q(z_1,z_2,y|x)} \log \frac{p(z_1|z_2,y)}{q(z_1|x)} = E_{q(z_1|x)} \left[\sum_y q(y|z_1) E_{q(z_2|z_1,y)} \big[\log \frac{p(z_1|z_2,y)}{q(z_1|x)} \big] \right] \tag{8}$$

$$E_{q(z_1,y|x)} \log \frac{p(y)}{q(y|z_1)} = E_{q(z_1|x)} \sum_y q(y|z_1) \log \frac{p(y)}{q(y|z_1)} \tag{9}$$

$$E_{q(z_1,z_2,y|x)} \log \frac{p(z_2)}{q(z_2|z_1,y)} = E_{q(z_1|x)} \left[\sum_y q(y|z_1) E_{q(z_2|z_1,y)} \big[\log \frac{p(z_2)}{q(z_2|z_1,y)} \big] \right] \tag{10}$$

2 Notes on the implementation

The VAE model in this project was implemented from scratch based on the ELBO loss derivation above. For part of the loss calculation, I imported the ZINB loss class from the scvi-tools package.