

### Problem formulation:

GEDI (Gene Expression Decomposition and Integration) is a framework for aligning multiple high-dimensional datasets while decomposing the data into biologically relevant components.

First, consider the simple decomposition of a single dataset using, for example, SVD:

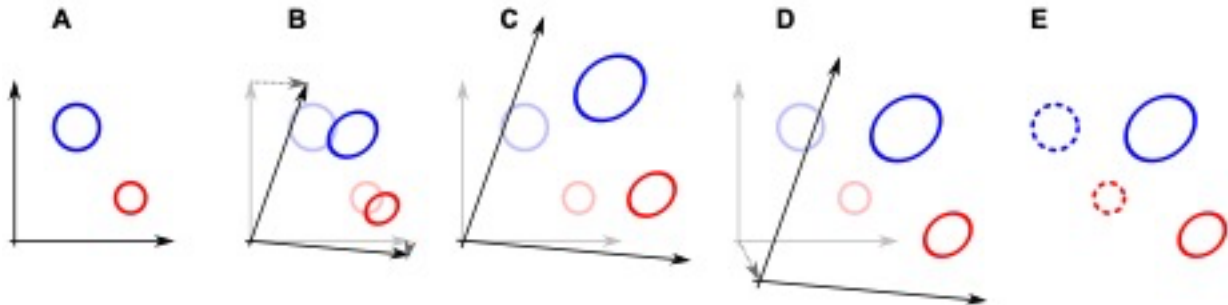
$$Y = USV^T$$

In this decomposition,  $U$  and  $V$  are orthonormal matrices. In GEDI, we may enforce orthogonality in some cases, but it may also arise as a byproduct of enforcing L2 shrinkage of the low rank matrices. More generally, we aim to decompose  $Y$  into lower rank matrices  $Z$  and  $B$ , such that:

$$Y = ZDB$$

Here,  $D$  is a diagonal matrix for normalization, which ensures each row of  $DB$  has exactly an L2 norm of 1. As we will describe below, we perform this decomposition while enforcing certain constraints on the L1 or L2 norm of the rows or columns of  $B$ , and also enforcing L2 shrinkage on  $Z$ . We can also optionally enforce orthogonality of  $Z$  by assuming  $Z=US$ , which generally improves integration results.

Now, let's consider the general problem of aligning two or more multi-dimensional datasets while performing joint low-rank decomposition. This is a non-trivial problem because different datasets are not necessarily provided in the same reference frame. The schematic below shows the concept:



Panel (A) shows a reference frame of coordinates from which all the data originated. However, each dataset deviates from this reference space through some operations: the axes may be distorted (B-C), and/or there may be an offset (D). The result will be datasets that do not overlap, because these operations can be different from one dataset to another. In reality, neither these operations nor the principal axes are known (E), and we want to infer them so that we can bring back the datasets into the same reference frame.

These operations can be expressed using the equation below, which connects the coordinates of each point in a given dataset to its coordinates in the reference frame:

$$y^T = o^T + (Q + Z)Db^T$$

In the equation above,  $Z$  is a  $G \times K$  matrix denoting the  $K$  principal axes of the reference frame (along the  $G$  genes), and  $b$  is a vector of length  $K$  that denotes the coordinates of a data point in this reference frame (e.g.  $K$  components in one cell).  $Q$  is a  $G \times K$  matrix that denotes the distortions to the principal axes of the reference frame, and  $o$  is the offset vector of length  $G$ . Finally,  $y$  is the vector of coordinates of the data point after these transformations.

If we have multiple datasets, with each dataset having multiple data points, we will have:

$$Y_i = \mathbf{o}_i^T \mathbf{j}_i + (\mathbf{Q}_i + \mathbf{Z}) \mathbf{D} \mathbf{B}_i$$

Here,  $Y_i$  is the  $G \times N$  matrix of post-transformation coordinates of the  $N_i$  data points in the  $i$ th dataset (e.g. the gene-by-cell expression matrix in dataset  $i$ ),  $\mathbf{j}_i$  is a vector of ones with a length of  $N_i$ ,  $\mathbf{o}_i$  is the offset vector for the  $i$ th dataset,  $\mathbf{Q}_i$  is the dataset-specific matrix of distortions,  $\mathbf{Z}$  is the matrix denoting the shared (reference) coordinate system, and  $\mathbf{B}_i$  is the matrix of coordinates of the data points in the  $i$ th dataset before transformation (i.e. relative to the reference coordinate system  $\mathbf{Z}$ ). The concatenation of all  $\mathbf{B}_i$  matrices results in matrix  $\mathbf{B} = [\mathbf{B}_1, \mathbf{B}_2, \dots, \mathbf{B}_n]$ , which is the coordinates of the data relative to the reference frame before all the transformations. This matrix can be interpreted as the result of “data integration”. Given  $\mathbf{Y} = [Y_1, Y_2, \dots, Y_n]$ , the matrix of data points across  $n$  datasets, we want to infer the other components of the model.

We note that  $\mathbf{Y}$  may also be affected by a shared “global offset”, i.e. gene-specific scaling factors, and by cell-specific scaling factors (a.k.a library size). Therefore, we have:

$$Y_i = \mathbf{o}_i^T \mathbf{j}_i + (\mathbf{Q}_i + \mathbf{Z}) \mathbf{D} \mathbf{B}_i + \tilde{\mathbf{o}}^T \mathbf{j}_i + \mathbf{j}'^T \mathbf{s}_i$$

Here,  $\mathbf{o}$  is the vector of gene-specific global offsets, and  $\mathbf{s}_i$  is the vector of cell-specific scaling factors.

Note that the transformations discussed above generally increase the variance of data along the principal axes. In other words, the datasets are maximally aligned when the variance of  $\mathbf{Z} \mathbf{D} \mathbf{B}$  is equal to the smallest variance of the individual datasets  $\mathbf{Z} \mathbf{D} \mathbf{B}_i$ . Therefore, we can expect that proper alignment leads to a decrease in the variance of  $\mathbf{Z} \mathbf{D} \mathbf{B}$ . Since  $\mathbf{D} \mathbf{B}$  is constrained so that each of its rows has an L2 norm of 1, the variance of  $\mathbf{Z} \mathbf{D} \mathbf{B}$  is minimized when the L2 norms the columns of  $\mathbf{Z}$  are minimized.

This framework also allows us to incorporate prior information about gene relatedness, in order to guide the identification of biologically relevant axes in the reference frame. We can do this by modeling  $\mathbf{Z}$  as a function of biological prior  $\mathbf{C}$ :

$$\mathbf{Z} \sim \mathbf{C} \times \mathbf{A}$$

where  $\mathbf{A}$  is a coefficient matrix that can be interpreted as the “activity” of each component of  $\mathbf{C}$  along each axis of  $\mathbf{Z}$ .

Similarly, we can have a prior  $\mathbf{H}$  for the distortion matrices  $\mathbf{Q}_i$ , connecting the distortions to gene-specific features such as length, GC content, chromosomal positions, etc:

$$\mathbf{Q}_i \sim \mathbf{H} \times \mathbf{R}_i$$

Our objective is to infer the model parameters  $\theta = \{\tilde{\mathbf{o}}, \mathbf{o}_i, \mathbf{s}_i, \mathbf{Q}_i, \mathbf{Z}, \mathbf{D}, \mathbf{B}, \mathbf{A}, \mathbf{R}_i\}$ , so as to (a) properly fit the model to the observed values  $\mathbf{Y}$ , (b) minimize the variance of  $\mathbf{Z}$ , (c) minimize the distortions that are required to achieve the previous two objectives, and (d) ensure that  $\mathbf{Z}$  and  $\mathbf{Q}_i$  are connected to our prior knowledge, if available. We can achieve these by reformulating the problem in a Bayesian framework, where each of the model parameters has a prior.

### Bayesian formulation of the model

The model parameters that need to be estimated are:

$$\theta = \{\tilde{\mathbf{o}}, \mathbf{o}_i, \mathbf{s}_i, \mathbf{Q}_i, \mathbf{Z}, \mathbf{D}, \mathbf{B}, \mathbf{A}, \mathbf{R}_i\}$$

We are interested in maximizing the likelihood of  $\theta$  given the observed expression values  $\mathbf{Y}$  (and priors  $\mathbf{C}$  and  $\mathbf{H}$ )

$$L(\theta; \mathbf{Y}, \mathbf{C}, \mathbf{H}) = P(\mathbf{Y}|\theta)P(\theta|\mathbf{C}, \mathbf{H})$$

We model  $\mathbf{Y}$  as a random variable with normal distribution:

$$\begin{aligned} \mathbf{Y}|\theta &\sim N(\hat{\mathbf{Y}}, \sigma^2 \mathbf{I}_{NJ}) \\ \hat{\mathbf{Y}}_i &= \tilde{\mathbf{o}}^T \mathbf{j}_i + \mathbf{o}_i^T \mathbf{j}_i + \mathbf{j}'^T \mathbf{s}_i + (\mathbf{Q}_i + \mathbf{Z})\mathbf{B}_i \end{aligned}$$

Therefore:

$$\begin{aligned} -\log P(\mathbf{Y}|\theta) &= \frac{NJ}{2} \log(2\pi\sigma^2) + \frac{1}{2\sigma^2} \sum_i \|\mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z})\mathbf{B}_i\|_2^2 \\ &= \frac{NJ}{2} \log(2\pi) + \frac{NJ}{2} \log(\sigma^2) \\ &\quad + \frac{1}{2\sigma^2} \sum_i \|\mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z})\mathbf{B}_i\|_2^2 \end{aligned}$$

Where  $\sigma^2$  is the variance of error,  $N$  is the number of cells and  $J$  is the number of genes.

Also, we can write the probability distribution of  $\theta$  as:

$$\begin{aligned} P(\theta|\mathbf{C}, \mathbf{H}) &= P(\tilde{\mathbf{o}}, \mathbf{o}_i, \mathbf{s}_i, \mathbf{Q}_i, \mathbf{Z}, \mathbf{B}, \mathbf{A}, \mathbf{R}_i|\mathbf{C}, \mathbf{H}) \\ &= P(\tilde{\mathbf{o}}) \times \prod_i P(\mathbf{s}_i) \times \prod_i P(\mathbf{o}_i) \times \prod_i P(\mathbf{Q}_i, \mathbf{R}_i|\mathbf{H}) \times P(\mathbf{Z}, \mathbf{A}|\mathbf{C}) \times P(\mathbf{B}) \end{aligned}$$

$$\begin{aligned} -\log P(\theta) &= -\log P(\tilde{\mathbf{o}}) - \sum_i \log P(\mathbf{s}_i) - \sum_i \log P(\mathbf{o}_i) - \sum_i \log P(\mathbf{Q}_i, \mathbf{R}_i|\mathbf{H}) - \log P(\mathbf{Z}, \mathbf{A}|\mathbf{C}) \\ &\quad - \log P(\mathbf{B}) \end{aligned}$$

Each of the independent probability distributions can be written as follows in the next sections:

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We assume that the global offsets and the cell-specific scaling factors have normal distributions around **an original (prior) point estimate obtained from data**:

$$\begin{aligned} \tilde{\mathbf{o}} &\sim N(\tilde{\mathbf{o}}_0, \sigma^2 S_{\tilde{\mathbf{o}}} \mathbf{I}) \\ \mathbf{s}_i &\sim N(\mathbf{s}_{i,0}, \sigma^2 S_{s,i} \mathbf{I}) \end{aligned}$$

This leads to:

$$\begin{aligned} -\log P(\tilde{\mathbf{o}}) &= \frac{J}{2} \log(2\pi\sigma^2 S_{\tilde{\mathbf{o}}}) + \frac{1}{2\sigma^2 S_{\tilde{\mathbf{o}}}} \|\tilde{\mathbf{o}} - \tilde{\mathbf{o}}_0\|_2^2 \\ &= \frac{J}{2} \log(2\pi S_{\tilde{\mathbf{o}}}) + \frac{J}{2} \log(\sigma^2) + \frac{1}{2\sigma^2 S_{\tilde{\mathbf{o}}}} \|\tilde{\mathbf{o}} - \tilde{\mathbf{o}}_0\|_2^2 \end{aligned}$$

Similarly:

$$\begin{aligned}
-\log P(\mathbf{s}_i) &= \frac{N_i}{2} \log(2\pi\sigma^2 S_{s,i}) + \frac{1}{2\sigma^2 S_{s,i}} \|\mathbf{s}_i - \mathbf{s}_{i,0}\|_2^2 \\
&= \frac{N_i}{2} \log(2\pi S_{s,i}) + \frac{N_i}{2} \log(\sigma^2) + \frac{1}{2\sigma^2 S_{s,i}} \|\mathbf{s}_i - \mathbf{s}_{i,0}\|_2^2
\end{aligned}$$

The multiplication factors that connect the variances of the priors to  $\sigma^2$ , i.e.  $S_o$  and  $S_{s,i}$ , are hyperparameters (the choice of these hyperparameters are discussed later).

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For the dataset-specific offsets, we assume each  $\mathbf{o}_i$  has a normal prior with variance proportional to  $\sigma^2$ . The multiplication factor that connects the variance of this prior to  $\sigma^2$  is a hyperparameter (the choice of this hyperparameters is discussed later):

$$\mathbf{o}_i \sim N(0, \sigma^2 S_{o,i} \mathbf{I})$$

This leads to:

$$-\log P(\mathbf{o}_i) = \frac{J}{2} \log(2\pi\sigma^2 S_{o,i}) + \frac{1}{2\sigma^2 S_{o,i}} \|\mathbf{o}_i\|_2^2 = \frac{J}{2} \log(2\pi S_{o,i}) + \frac{J}{2} \log(\sigma^2) + \frac{1}{2\sigma^2 S_{o,i}} \|\mathbf{o}_i\|_2^2$$

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For the dataset-specific distortion matrices, we assume  $\mathbf{Q}_i$  has a normal prior with the mean  $\mathbf{H}\mathbf{R}_i$  and variance proportional to  $\sigma^2$ . Similarly,  $\mathbf{R}_i$  has a normal prior with mean zero and variance proportional to the variance of  $\mathbf{Q}_i$ . The multiplication factors that connect the variances of these priors to  $\sigma^2$  are hyperparameters (the choice of this hyperparameters is discussed later):

$$\begin{aligned}
P(\mathbf{Q}_i, \mathbf{R}_i | \mathbf{H}) &= P(\mathbf{Q}_i | \mathbf{R}_i, \mathbf{H}) P(\mathbf{R}_i) \\
\mathbf{Q}_i | \mathbf{R}_i, \mathbf{H} &\sim N(\mathbf{H}\mathbf{R}_i, \sigma^2 S_{Q,i} \mathbf{I}) \\
\mathbf{R}_i &\sim N(0, \sigma^2 S_{Q,i} S_{R,i} \mathbf{I})
\end{aligned}$$

This leads to:

$$\begin{aligned}
-\log P(\mathbf{Q}_i, \mathbf{R}_i | \mathbf{H}) &= \frac{JK}{2} \log(2\pi\sigma^2 S_{Q,i}) + \frac{1}{2\sigma^2 S_{Q,i}} \|\mathbf{Q}_i - \mathbf{H}\mathbf{R}_i\|_2^2 + \frac{LK}{2} \log(2\pi\sigma^2 S_{Q,i} S_{R,i}) \\
&\quad + \frac{1}{2\sigma^2 S_{Q,i} S_{R,i}} \|\mathbf{R}_i\|_2^2 \\
&= \frac{JK}{2} \log(2\pi S_{Q,i}) + \frac{LK}{2} \log(2\pi S_{Q,i} S_{R,i}) + \frac{K}{2} (J + L) \log(\sigma^2) \\
&\quad + \frac{1}{2\sigma^2 S_{Q,i}} \|\mathbf{Q}_i - \mathbf{H}\mathbf{R}_i\|_2^2 + \frac{1}{2\sigma^2 S_{Q,i} S_{R,i}} \|\mathbf{R}_i\|_2^2
\end{aligned}$$

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For the common coordinate matrix, we assume  $\mathbf{Z}$  has a normal prior with the mean  $\mathbf{C}\mathbf{A}$  and variance proportional to  $\sigma^2$ . Similarly,  $\mathbf{A}$  has a normal prior with mean zero and variance proportional to the variance of  $\mathbf{Z}$ . The multiplication factors that connect the variances of these priors to  $\sigma^2$  are hyperparameters (the choice of this hyperparameters is discussed later):

$$\begin{aligned}
P(\mathbf{Z}, \mathbf{A} | \mathbf{C}) &= P(\mathbf{Z} | \mathbf{A}, \sigma^2, \mathbf{C}) P(\mathbf{A} | \sigma^2) \\
\mathbf{Z} | \mathbf{A}, \mathbf{C} &\sim N(\mathbf{C}\mathbf{A}, \sigma^2 S_Z \mathbf{I})
\end{aligned}$$

$$\mathbf{A} \sim N(0, \sigma^2 S_Z S_A \mathbf{I})$$

This leads to:

$$\begin{aligned} -\log P(\mathbf{Z}, \mathbf{A} | \mathbf{C}) &= \frac{JK}{2} \log(2\pi\sigma^2 S_Z) + \frac{1}{2\sigma^2 S_Z} \|\mathbf{Z} - \mathbf{CA}\|_2^2 + \frac{PK}{2} \log(2\pi\sigma^2 S_Z S_A) + \frac{1}{2\sigma^2 S_Z S_A} \|\mathbf{A}\|_2^2 \\ &= \frac{JK}{2} \log(2\pi S_Z) + \frac{PK}{2} \log(2\pi S_Z S_A) + \frac{K}{2} (J + P) \log(\sigma^2) + \frac{1}{2\sigma^2 S_Z} \|\mathbf{Z} - \mathbf{CA}\|_2^2 \\ &\quad + \frac{1}{2\sigma^2 S_Z S_A} \|\mathbf{A}\|_2^2 \end{aligned}$$

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Finally, for solving  $\mathbf{B}$ , we assume that  $\mathbf{B}$  is restricted to a subspace or manifold, depending on the type of restriction (L2 norm restriction, clustering-like restriction, or hyperellipsoid restriction). Within that restricted subspace or manifold, which we call the subspace  $\mathbb{B}$ ,  $\mathbf{B}$  has a uniform prior distribution. In other words:

$$P(\mathbf{B}) = U(\mathbb{B})$$

This means that log-likelihood of this uniform prior is always constant within the subspace  $\mathbb{B}$ , and can be ignored.

#### Solving $\mathbf{B}_i$ :

For every dataset  $i$ , we separately solve  $\mathbf{B}_i$  as described in the previous version of this document.

#### Solving $\mathbf{D}$ :

$\mathbf{D}$  is simply a diagonal matrix that ensures the L2 norm of each row of  $\mathbf{DB}$  is equal to 1.

#### Solving $\mathbf{Z}$ :

We solve  $\mathbf{Z}$  as:

$$\begin{aligned} \operatorname{argmin}_{\mathbf{Z}} & \left\{ \frac{1}{2\sigma^2} \sum_i \|\mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z}) \mathbf{DB}_i\|_2^2 + \frac{1}{2\sigma^2 S_Z} \|\mathbf{Z} - \mathbf{CA}\|_2^2 \right\} \\ &= \operatorname{argmin}_{\mathbf{Z}} \left\{ \sum_i \|\mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z}) \mathbf{DB}_i\|_2^2 + \frac{1}{S_Z} \|\mathbf{Z} - \mathbf{CA}\|_2^2 \right\} \end{aligned}$$

When  $\mathbf{Z}$  is not restricted to be orthogonal, we can simply solve it as:

$$\mathbf{Z} = \left( \mathbf{Y}' (\mathbf{DB})^T + \frac{1}{S_Z} \mathbf{CA} \right) \left( (\mathbf{DB})(\mathbf{DB})^T + \frac{1}{S_Z} \mathbf{I} \right)^{-1}$$

where

$$\begin{aligned} \mathbf{Y}'_i &= \mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - \mathbf{Q}_i \mathbf{DB}_i \\ \mathbf{Y}' &= [\mathbf{Y}'_1 \quad \dots \quad \mathbf{Y}'_n] \\ \mathbf{B} &= [\mathbf{B}_1 \quad \dots \quad \mathbf{B}_n] \end{aligned}$$

If no prior matrix  $\mathbf{C}$  is provided, then we have:

$$\begin{aligned}
& \operatorname{argmin}_{\mathbf{Z}} \left\{ \frac{1}{2\sigma^2} \sum_i \|\mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z}) \mathbf{D} \mathbf{B}_i\|_2^2 + \frac{1}{2\sigma^2 S_Z} \|\mathbf{Z}\|_2^2 \right\} \\
&= \operatorname{argmin}_{\mathbf{Z}} \left\{ \sum_i \|\mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z}) \mathbf{D} \mathbf{B}_i\|_2^2 + \frac{1}{S_Z} \|\mathbf{Z}\|_2^2 \right\} \\
&= \mathbf{Y}' (\mathbf{D} \mathbf{B})^T \left( (\mathbf{D} \mathbf{B}) (\mathbf{D} \mathbf{B})^T + \frac{1}{S_Z} \mathbf{I} \right)^{-1}
\end{aligned}$$

When  $\mathbf{Z}$  is restricted to be orthogonal (but not orthonormal), then we have:

$$\begin{aligned}
& \operatorname{argmin}_{\mathbf{Z}} \left\{ \frac{1}{2\sigma^2} \sum_i \|\mathbf{Y}'_i - \mathbf{Z} \mathbf{D} \mathbf{B}_i\|_2^2 + \frac{1}{2\sigma^2 S_Z} \|\mathbf{Z} - \mathbf{C} \mathbf{A}\|_2^2 \right\} \\
&= \operatorname{argmin}_{\mathbf{Z}} \left\{ \sum_i \|\mathbf{Y}'_i - \mathbf{U} \mathbf{S} \mathbf{D} \mathbf{B}_i\|_2^2 + \frac{1}{S_Z} \|\mathbf{U} \mathbf{S} - \mathbf{C} \mathbf{A}\|_2^2 \right\}
\end{aligned}$$

where  $\mathbf{U}$  is an orthonormal matrix, and  $\mathbf{S}$  is a diagonal matrix. We can solve  $\mathbf{U}$  and  $\mathbf{S}$  separately in our block coordinate descent algorithm by treating them as separate blocks:

Solving  $\mathbf{S}$ :

To solve  $\mathbf{S}$ , we want to obtain:

$$\begin{aligned}
& \operatorname{argmin}_{\mathbf{S}} \left\{ \sum_i \|\mathbf{Y}'_i - \mathbf{U} \mathbf{S} \mathbf{D} \mathbf{B}_i\|_2^2 + \frac{1}{S_Z} \|\mathbf{U} \mathbf{S} - \mathbf{C} \mathbf{A}\|_2^2 \right\} \\
& \sum_i \|\mathbf{Y}'_i - \mathbf{U} \mathbf{S} \mathbf{D} \mathbf{B}_i\|_2^2 + \frac{1}{S_Z} \|\mathbf{U} \mathbf{S} - \mathbf{C} \mathbf{A}\|_2^2 = \sum_i \|\mathbf{Y}'_i - \mathbf{U} \mathbf{S} \mathbf{D} \mathbf{B}_i\|_2^2 + \left\| \frac{1}{\sqrt{S_Z}} \mathbf{U} \mathbf{S} - \frac{1}{\sqrt{S_Z}} \mathbf{C} \mathbf{A} \right\|_2^2 \\
&= \|\mathbf{Y}' - \mathbf{U} \mathbf{S} \mathbf{B}'\|_2^2
\end{aligned}$$

where:

$$\begin{aligned}
\mathbf{Y}' &= \begin{bmatrix} \mathbf{Y}'_1 & \mathbf{Y}'_2 & \dots & \mathbf{Y}'_n & \frac{1}{\sqrt{S_Z}} \mathbf{C} \mathbf{A} \end{bmatrix} \\
\mathbf{B}' &= \begin{bmatrix} \mathbf{D} \mathbf{B}_1 & \mathbf{D} \mathbf{B}_2 & \dots & \mathbf{D} \mathbf{B}_n & \frac{1}{\sqrt{S_Z}} \mathbf{I} \end{bmatrix}
\end{aligned}$$

Then, assuming that  $\mathbf{U}$  is given, we can solve  $\mathbf{S}$  as follows:

$$\begin{aligned}
& \operatorname{argmin}_{\mathbf{S}} \|\mathbf{Y}' - \mathbf{U} \mathbf{S} \mathbf{B}'\|_2^2 \\
& \operatorname{argmin}_{\mathbf{S}} \sum_j \sum_n \left( y'_{j,n} - \sum_k u_{j,k} s_k b'_{k,n} \right)^2 \\
&= \operatorname{argmin}_{\mathbf{S}} \sum_j \sum_n (y'_{j,n})^2 - 2 \sum_j \sum_n \left( y'_{j,n} \sum_k u_{j,k} s_k b'_{k,n} \right) \\
& \quad + \sum_j \sum_n \left( \sum_k u_{j,k} s_k b'_{k,n} \right)^2
\end{aligned}$$

For each element  $s_k$ , we can then separately solve as follows:

$$\begin{aligned}
& \frac{d}{d(s_\kappa)} \left[ \sum_j \sum_n (y'_{j,n})^2 - 2 \sum_j \sum_n \left( y'_{j,n} \sum_k u_{j,k} s_k b'_{k,n} \right) + \sum_j \sum_n \left( \sum_k u_{j,k} s_k b'_{k,n} \right)^2 \right] \\
& = -2 \sum_j \sum_n (y'_{j,n} u_{j,\kappa} b'_{\kappa,n}) + 2 \sum_j \sum_n u_{j,\kappa} b'_{\kappa,n} \sum_k u_{j,k} s_k b'_{k,n} = 0 \\
& - \sum_j \sum_n (y'_{j,n} u_{j,\kappa} b'_{\kappa,n}) + s_\kappa \sum_j \sum_n (u_{j,\kappa} b'_{\kappa,n})^2 + \sum_j \sum_n u_{j,\kappa} b'_{\kappa,n} \sum_{k \neq \kappa} u_{j,k} s_k b'_{k,n} = 0
\end{aligned}$$

Which can be rearranged as:

$$\begin{aligned}
s_\kappa \sum_j \sum_n (u_{j,\kappa} b'_{\kappa,n})^2 &= \sum_j \sum_n (y'_{j,n} u_{j,\kappa} b'_{\kappa,n}) - \sum_j \sum_n u_{j,\kappa} b'_{\kappa,n} \sum_{k \neq \kappa} u_{j,k} s_k b'_{k,n} \\
s_\kappa &= \frac{\sum_j \sum_n (y'_{j,n} u_{j,\kappa} b'_{\kappa,n}) - \sum_j \sum_n u_{j,\kappa} b'_{\kappa,n} \sum_{k \neq \kappa} u_{j,k} s_k b'_{k,n}}{\sum_j \sum_n (u_{j,\kappa} b'_{\kappa,n})^2} \\
&= \frac{\sum_j \sum_n (y'_{j,n} u_{j,\kappa} b'_{\kappa,n}) - \sum_n \sum_{k \neq \kappa} b'_{\kappa,n} s_k b'_{k,n} \sum_j u_{j,\kappa} u_{j,k}}{\sum_j \sum_n (u_{j,\kappa} b'_{\kappa,n})^2}
\end{aligned}$$

Then, considering the fact that the different columns of  $\mathbf{U}$  are orthonormal, and therefore their dot products are zero, this equation simplifies to:

$$\begin{aligned}
s_\kappa &= \frac{\sum_j \sum_n (y'_{j,n} u_{j,\kappa} b'_{\kappa,n})}{\sum_j \sum_n (u_{j,\kappa} b'_{\kappa,n})^2} = \frac{\sum_j u_{j,\kappa} \sum_n b'_{\kappa,n} y'_{j,n}}{\sum_n (b'_{\kappa,n})^2 \sum_j (u_{j,\kappa})^2} = \frac{\sum_j u_{j,\kappa} \sum_n b'_{\kappa,n} y'_{j,n}}{\sum_n (b'_{\kappa,n})^2} = \frac{\sum_j u_{j,\kappa} \sum_n b'_{\kappa,n} y'_{j,n}}{1 + \frac{1}{S_\Sigma}} \\
&= \frac{\sum_j u_{j,\kappa} [\mathbf{Y}'(\mathbf{B}')^T]_{j,\kappa}}{1 + \frac{1}{S_\Sigma}}
\end{aligned}$$

Solving  $\mathbf{U}$ :

$$\arg \min_{\mathbf{U}} \|\mathbf{Y}' - \mathbf{U} \mathbf{S} \mathbf{B}'\|_2^2$$

Assuming that  $\mathbf{S}$  is given, this problem transforms into a Procrustes problem. Therefore, we can solve  $\mathbf{U}$  by performing SVD on  $\mathbf{Y}'(\mathbf{S} \mathbf{B}')^T$ :

$$\begin{aligned}
\text{SVD}[\mathbf{Y}'(\mathbf{S} \mathbf{B}')^T] &= \mathbf{U}' \mathbf{S}' \mathbf{V}'^T \\
\mathbf{U} &= \mathbf{U}' \mathbf{V}'^T
\end{aligned}$$

Solving  $\mathbf{A}$ :

We solve  $\mathbf{A}$  as:

$$\begin{aligned}
\mathbf{A} &= \arg \min_{\mathbf{A}} \left\{ \frac{1}{2\sigma^2 S_Z} \|\mathbf{Z} - \mathbf{C} \mathbf{A}\|_2^2 + \frac{1}{2\sigma^2 S_Z S_A} \|\mathbf{A}\|_2^2 \right\} = \arg \min_{\mathbf{A}} \left\{ \|\mathbf{Z} - \mathbf{C} \mathbf{A}\|_2^2 + \frac{1}{S_A} \|\mathbf{A}\|_2^2 \right\} \\
&= \left( \mathbf{C}^T \mathbf{C} + \frac{1}{S_A} \mathbf{I} \right)^{-1} \mathbf{C}^T \mathbf{Z}
\end{aligned}$$

Solving  $\mathbf{Q}_i$ :

For each dataset  $i$ , we separately solve  $\mathbf{Q}_i$  as:

$$\begin{aligned}
& \operatorname{argmin}_{\mathbf{Q}_i} \left\{ \frac{1}{2\sigma^2} \|\mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z}) \mathbf{D} \mathbf{B}_i\|_2^2 + \frac{1}{2\sigma^2 S_{Q,i}} \|\mathbf{Q}_i - \mathbf{H} \mathbf{R}_i\|_2^2 \right\} \\
&= \operatorname{argmin}_{\mathbf{Q}_i} \left\{ \|\mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z}) \mathbf{D} \mathbf{B}_i\|_2^2 + \frac{1}{S_{Q,i}} \|\mathbf{Q}_i - \mathbf{H} \mathbf{R}_i\|_2^2 \right\} \\
&= \left( \mathbf{Y}'_i (\mathbf{D} \mathbf{B}_i)^T + \frac{1}{S_{Q,i}} \mathbf{H} \mathbf{R}_i \right) \left( (\mathbf{D} \mathbf{B}_i) (\mathbf{D} \mathbf{B}_i)^T + \frac{1}{S_{Q,i}} \mathbf{I} \right)^{-1}
\end{aligned}$$

where

$$\mathbf{Y}'_i = \mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - \mathbf{Z} \mathbf{D} \mathbf{B}_i$$

If no prior  $\mathbf{H}$  is provided, then we have:

$$\begin{aligned}
& \operatorname{argmin}_{\mathbf{Q}_i} \left\{ \frac{1}{2\sigma^2} \|\mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z}) \mathbf{D} \mathbf{B}_i\|_2^2 + \frac{1}{2\sigma^2 S_{Q,i}} \|\mathbf{Q}_i\|_2^2 \right\} \\
&= \mathbf{Y}'_i (\mathbf{D} \mathbf{B}_i)^T \left( (\mathbf{D} \mathbf{B}_i) (\mathbf{D} \mathbf{B}_i)^T + \frac{1}{S_{Q,i}} \mathbf{I} \right)^{-1}
\end{aligned}$$

Solving  $\mathbf{R}_i$ :

For each dataset  $i$ , we solve  $\mathbf{R}_i$  as:

$$\begin{aligned}
\mathbf{R}_i &= \operatorname{argmin}_A \left\{ \frac{1}{2\sigma^2 S_{Q,i}} \|\mathbf{Q}_i - \mathbf{H} \mathbf{R}_i\|_2^2 + \frac{1}{2\sigma^2 S_{Q,i} S_{R,i}} \|\mathbf{R}_i\|_2^2 \right\} \\
&= \operatorname{argmin}_A \left\{ \|\mathbf{Q}_i - \mathbf{H} \mathbf{R}_i\|_2^2 + \frac{1}{S_{R,i}} \|\mathbf{R}_i\|_2^2 \right\} = \left( \mathbf{H}^T \mathbf{H} + \frac{1}{S_{R,i}} \mathbf{I} \right)^{-1} \mathbf{H}^T \mathbf{Q}_i
\end{aligned}$$

Solving  $\mathbf{o}_i$ :

For every dataset  $i$ , we solve  $\mathbf{o}_i$  as:

$$\begin{aligned}
& \operatorname{argmin}_{\mathbf{o}_i} \left\{ \frac{1}{2\sigma^2} \sum_i \|\mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z}) \mathbf{B}_i\|_2^2 + \frac{1}{2\sigma^2 S_{o,i}} \|\mathbf{o}_i\|_2^2 \right\} \\
&= \operatorname{argmin}_{\mathbf{o}_i} \left\{ \sum_i \|\mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z}) \mathbf{B}_i\|_2^2 + \frac{1}{S_{o,i}} \|\mathbf{o}_i\|_2^2 \right\} \\
&= \left( \frac{\mathbf{Y}'_i \times \mathbf{j}_i^T}{N_i + \frac{1}{S_{o,i}}} \right)^T
\end{aligned}$$

where:

$$\mathbf{Y}'_i = \mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z}) \mathbf{B}_i$$

Solving the global offset:



$$\begin{aligned}\tilde{\mathbf{o}} &= \operatorname{argmin}_{\tilde{\mathbf{o}}} \left\{ \frac{1}{2\sigma^2} \sum_i \|\mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z}) \mathbf{B}_i\|_2^2 + \frac{1}{2\sigma^2 S_{\tilde{\mathbf{o}}}} \|\tilde{\mathbf{o}} - \tilde{\mathbf{o}}_0\|_2^2 \right\} \\ &= \frac{(\mathbf{Y}' \times \mathbf{j}^T)^T + \frac{1}{S_{\tilde{\mathbf{o}}}} \tilde{\mathbf{o}}_0}{N + \frac{1}{S_{\tilde{\mathbf{o}}}}}\end{aligned}$$

where

$$\begin{aligned}\mathbf{Y}'_i &= \mathbf{Y}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z}) \mathbf{B}_i \\ \mathbf{Y}' &= [\mathbf{Y}'_1 \quad \dots \quad \mathbf{Y}'_n]\end{aligned}$$

Solving the cell-specific library sizes:

$$\begin{aligned}\mathbf{s}_i &= \operatorname{argmin}_{\mathbf{s}_i} \left\{ \frac{1}{2\sigma^2} \|\mathbf{Y}_i - \tilde{\mathbf{o}}^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{j}'^T \mathbf{s}_i - (\mathbf{Q}_i + \mathbf{Z}) \mathbf{B}_i\|_2^2 + \frac{1}{2\sigma^2 S_{s,i}} \|\mathbf{s}_i - \mathbf{s}_{i,0}\|_2^2 \right\} \\ &= \frac{\mathbf{j}' \times \mathbf{Y}'_i + \frac{1}{S_{s,i}} \mathbf{s}_{i,0}}{J + \frac{1}{S_{s,i}}}\end{aligned}$$

where

$$\mathbf{Y}'_i = \mathbf{Y}_i - \mathbf{o}_i^T \mathbf{j}_i - \mathbf{o}_i^T \mathbf{j}_i - (\mathbf{Q}_i + \mathbf{Z}) \mathbf{B}_i$$

Solving  $\sigma^2$

When  $\mathbf{Y}$  is observed, since  $\sigma^2$  does not appear in any of the equations for solving other model parameters, there is no need to estimate it.

Choice of hyperparameters

--

For the variance of  $\mathbf{Z}$ , as we have shown previously, under the null model we have:

$$\sigma_{Z,0}^2 = \sigma_0^2$$

Therefore:

$$S_Z = 1$$

--

For the variance of  $\mathbf{Q}_i$ , as we have shown previously, under the null model we have:

$$\sigma_{Q_i,0}^2 = \sigma_0^2 \frac{N}{N_i}$$

Therefore:

$$S_{Q,i} = \frac{N}{N_i}$$

--

For the variance of  $\mathbf{A}$ , as we have shown previously, under the null model we have:

$$\sigma_{A,0}^2 = \frac{\sigma_{Z,0}^2}{\frac{\|\mathbf{C}\|_2^2}{P}} = \sigma_{Z,0}^2 \frac{P}{\|\mathbf{C}\|_2^2}$$

Therefore:

$$S_A = \frac{P}{\|\mathbf{C}\|_2^2}$$

--

For the variance of  $\mathbf{R}_i$ , as we have shown previously, under the null model we have:

$$\sigma_{Ri,0}^2 = \frac{\sigma_{Qi,0}^2}{\frac{\|\mathbf{H}\|_2^2}{L}} = \sigma_{Qi,0}^2 \times \frac{L}{\|\mathbf{H}\|_2^2}$$

Therefore:

$$S_{R,i} = \frac{L}{\|\mathbf{H}\|_2^2}$$

--

For the variance of  $\mathbf{o}_i$ , as we have shown previously, under the null model we have:

$$\sigma_{oi,0}^2 = \frac{\sigma_0^2}{N_i}$$

Therefore:

$$S_{o,i} = \frac{1}{N_i}$$

Similarly:

$$S_{\tilde{o}} = \frac{1}{N}$$

And:

$$S_{s,i} = \frac{1}{J}$$

### **Extension of the model to directly handle count data**

We can modify this model to directly fit to count data, with an appropriate distribution for the counts. Here, we consider the case where the counts, represented by matrix  $\mathbf{M}$  ( $M_i$  for each individual dataset  $i$ ) follow a Poisson distribution with the mean of the distribution equal to the exponential of a latent variable  $\mathbf{Y}$  ( $Y_i$  for each individual dataset  $i$ ). The latent variable  $\mathbf{Y}$  itself has a normal distribution around the values predicted by the model. Therefore:

$$\begin{aligned}\hat{\mathbf{Y}}_i &= \tilde{\mathbf{o}}^T \mathbf{j}_i + \mathbf{o}_i^T \mathbf{j}_i + \mathbf{j}'^T \mathbf{s}_i + (\mathbf{Q}_i + \mathbf{Z}) \mathbf{D} \mathbf{B}_i \\ \hat{\mathbf{Y}} &= [\hat{\mathbf{Y}}_1 \quad \dots \quad \hat{\mathbf{Y}}_n] \\ \mathbf{Y} &\sim N(\hat{\mathbf{Y}}, \sigma^2 \mathbf{I}) \\ \mathbf{M} &\sim \text{Pois}(\mathbf{e}^{\mathbf{Y}})\end{aligned}$$

In other words,  $\mathbf{M}$  has a log-normal-Poisson distribution with parameters  $\hat{\mathbf{Y}}$  and  $\sigma^2$ . Note that now the likelihood function has this form:

$$L(\theta; \mathbf{M}, \mathbf{C}, \mathbf{H}) = P(\mathbf{M}|\theta)P(\theta|\mathbf{C}, \mathbf{H}) = \int P(\mathbf{M}|\mathbf{Y})P(\mathbf{Y}|\theta)P(\theta|\mathbf{C}, \mathbf{H})d\mathbf{Y}$$

We will use expectation maximization to solve this problem, where at each iteration we obtain the expected value of the log likelihood function of  $\theta$  over the conditional distribution of  $\mathbf{Y}$  given  $\mathbf{M}$  and the current estimates of  $\theta^{(t)}$ , followed by finding an updated  $\theta$  that maximizes the expected log likelihood:

$$\begin{aligned} Q(\theta|\theta^{(t)}) &= E_{\mathbf{Y}|\mathbf{M}, \theta^{(t)}}[\log L(\theta; \mathbf{M}, \mathbf{C}, \mathbf{H})] \\ &= \int [\log P(\mathbf{M}|\mathbf{Y}) + \log P(\mathbf{Y}|\theta) + \log P(\theta|\mathbf{C}, \mathbf{H})]P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} \\ &= \int \log P(\mathbf{M}|\mathbf{Y})P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} + \int \log P(\mathbf{Y}|\theta)P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} \\ &\quad + \int \log P(\theta|\mathbf{C}, \mathbf{H})P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} \\ &= \int \log P(\mathbf{M}|\mathbf{Y})P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} + \int \log P(\mathbf{Y}|\theta)P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} \\ &\quad + \log P(\theta|\mathbf{C}, \mathbf{H}) \int P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} \\ &= \int \log P(\mathbf{M}|\mathbf{Y})P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} + \int \log P(\mathbf{Y}|\theta)P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} \\ &\quad + \log P(\theta|\mathbf{C}, \mathbf{H}) \end{aligned}$$

Since the first part of the three parts does not depend on  $\theta$ , in the M step we need to obtain:

$$\arg \max_{\theta} Q(\theta|\theta^{(t)}) = \arg \max_{\theta} \left[ \int \log P(\mathbf{Y}|\theta)P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} + \log P(\theta|\mathbf{C}, \mathbf{H}) \right]$$

We have previously discussed  $\log P(\theta|\mathbf{C}, \mathbf{H})$  and how it can be incorporated into a block coordinate descent algorithm. For the integral, we have:

$$\begin{aligned} \int \log P(\mathbf{Y}|\theta)P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} &= \int \left[ \frac{NJ}{2} \log(2\pi\sigma^2) + \frac{1}{2\sigma^2} \|\mathbf{Y} - \hat{\mathbf{Y}}(\theta)\|_2^2 \right] P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} \\ &= \frac{NJ}{2} \log(2\pi\sigma^2) + \frac{1}{2\sigma^2} \int \|\mathbf{Y} - \hat{\mathbf{Y}}(\theta)\|_2^2 P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} \\ &= \frac{NJ}{2} \log(2\pi\sigma^2) + \frac{1}{2\sigma^2} \sum_j \sum_n \int (y_{j,n} - \hat{y}_{j,n})^2 P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} \\ &= \frac{NJ}{2} \log(2\pi\sigma^2) + \frac{1}{2\sigma^2} \sum_j \sum_n \int (y_{j,n}^2 - 2y_{j,n}\hat{y}_{j,n} + \hat{y}_{j,n}^2) P(\mathbf{Y}|\mathbf{M}, \theta^{(t)})d\mathbf{Y} \\ &= \frac{NJ}{2} \log(2\pi\sigma^2) + \frac{1}{2\sigma^2} \sum_j \sum_n \left[ E_{\mathbf{Y}|\mathbf{M}, \theta^{(t)}}(y_{j,n}^2) - 2\hat{y}_{j,n} E_{\mathbf{Y}|\mathbf{M}, \theta^{(t)}}(y_{j,n}) + \hat{y}_{j,n}^2 \right] \end{aligned}$$

If we consider that:

$$\begin{aligned} \text{Var}(y_{j,n}|\mathbf{M}, \theta^{(t)}) &= E_{\mathbf{Y}|\mathbf{M}, \theta^{(t)}}(y_{j,n}^2) - \left[ E_{\mathbf{Y}|\mathbf{M}, \theta^{(t)}}(y_{j,n}) \right]^2 \\ \Rightarrow E_{\mathbf{Y}|\mathbf{M}, \theta^{(t)}}(y_{j,n}^2) &= \text{Var}(y_{j,n}|\mathbf{M}, \theta^{(t)}) + \left[ E_{\mathbf{Y}|\mathbf{M}, \theta^{(t)}}(y_{j,n}) \right]^2 \end{aligned}$$

Then we can write:

$$\begin{aligned}
& \int \log P(\mathbf{Y}|\theta) P(\mathbf{Y}|\mathbf{M}, \theta^{(t)}) d\mathbf{Y} \\
&= \frac{NJ}{2} \log(2\pi\sigma^2) \\
&+ \frac{1}{2\sigma^2} \sum_j \sum_n \left[ \text{Var}(y_{j,n}|\mathbf{M}, \theta^{(t)}) + \left[ E_{\mathbf{Y}|\mathbf{M}, \theta^{(t)}}(y_{j,n}) \right]^2 - 2\hat{y}_{j,n} E_{\mathbf{Y}|\mathbf{M}, \theta^{(t)}}(y_{j,n}) \right. \\
&\quad \left. + \hat{y}_{j,n}^2 \right] \\
&= \frac{NJ}{2} \log(2\pi\sigma^2) + \frac{1}{2\sigma^2} \sum_j \sum_n \text{Var}(y_{j,n}|\mathbf{M}, \theta^{(t)}) \\
&+ \frac{1}{2\sigma^2} \sum_j \sum_n \left[ E(y_{j,n}|\mathbf{M}, \theta^{(t)}) - \hat{y}_{j,n} \right]^2
\end{aligned}$$

Note that only the last part depends on  $\theta$  (since  $\hat{y}_{j,n}$  is a function of  $\theta$ ). Therefore:

$$\arg \max_{\theta} Q(\theta|\theta^{(t)}) = \arg \max_{\theta} \frac{1}{2\sigma^2} \|\mathbf{E}(\mathbf{Y}|\mathbf{M}, \theta^{(t)}) - \hat{\mathbf{Y}}(\theta)\|_2^2 + \log P(\theta|\mathbf{C}, \mathbf{H})$$

In other words, given  $\mathbf{M}$  and the current values of  $\theta$ , we first need to calculate the expectation of the latent variable  $\mathbf{Y}$ , and then use the same block coordinate descent procedure described in the previous section to obtain an updated  $\theta$  that maximizes  $Q$ .

#### Calculating the expectation:

The expected value of each element  $(j,n)$  of  $\mathbf{Y}$  (i.e. expression of the gene  $j$  in cell  $n$ ) is:

$$E(y_{j,n}|\mathbf{m}_{j,n}, \hat{y}_{j,n}) = \int_{-\infty}^{+\infty} P(y|\mathbf{m}_{j,n}, \hat{y}_{j,n}) y dy$$

where  $P(y|\mathbf{m}_{j,n}, \hat{y}_{j,n})$  is the posterior probability of  $y$  given the counts  $\mathbf{m}_{j,n}$  and the model:

$$\begin{aligned}
P(y|\mathbf{m}_{j,n}, \hat{y}_{j,n}) &= \frac{P(y, \mathbf{m}_{j,n}, \hat{y}_{j,n})}{P(\mathbf{m}_{j,n}, \hat{y}_{j,n})} = \frac{P(\mathbf{m}_{j,n}|y)P(y|\hat{y}_{j,n})P(\hat{y}_{j,n})}{P(\mathbf{m}_{j,n}, \hat{y}_{j,n})} \\
&= \frac{P(\hat{y}_{j,n})}{P(\mathbf{m}_{j,n}, \hat{y}_{j,n})} \times \frac{(e^y)^{m_{j,n}} e^{-e^y}}{m_{j,n}!} \times \frac{e^{-\frac{1}{2\sigma^2}(y-\hat{y}_{j,n})^2}}{\sigma\sqrt{2\pi}}
\end{aligned}$$

This leads to:

$$E(y_{j,n}|\mathbf{m}_{j,n}, \hat{y}_{j,n}) = c \int_{-\infty}^{+\infty} (e^y)^{m_{j,n}} e^{-e^y} e^{-\frac{1}{2\sigma^2}(y-\hat{y}_{j,n})^2} y dy = c \int_{-\infty}^{+\infty} e^{ym_{j,n}-e^y-\frac{1}{2\sigma^2}(y-\hat{y}_{j,n})^2} y dy$$

where  $c$  is a normalizing factor.

We use Laplace's method to approximate this integral (in Laplace's method, the posterior mean is equal to posterior mode), which leads to:

$$\begin{aligned}
E(y_{j,n}|\mathbf{m}_{j,n}, \hat{y}_{j,n}) &= \arg \max_y \left\{ ym_{j,n} - e^y - \frac{1}{2\sigma^2} (y - \hat{y}_{j,n})^2 \right\} \\
&= \arg \max_y \left\{ 2\sigma^2 ym_{j,n} - 2\sigma^2 e^y - (y - \hat{y}_{j,n})^2 \right\}
\end{aligned}$$

By setting the first derivative to zero, we have:

$$\begin{aligned} 2\sigma^2 m_{j,n} - 2\sigma^2 e^y - 2(y - \hat{y}_{j,n}) &= 0 \\ \sigma^2 e^y + y - (\hat{y}_{j,n} + \sigma^2 m_{j,n}) &= 0 \\ y &= -W(\sigma^2 e^{\hat{y}_{j,n} + \sigma^2 m_{j,n}}) + \hat{y}_{j,n} + \sigma^2 m_{j,n} \end{aligned}$$

Therefore:

$$E(y_{j,n} | m_{j,n}, \hat{y}_{j,n}) = -W(\sigma^2 e^{\hat{y}_{j,n} + \sigma^2 m_{j,n}}) + \hat{y}_{j,n} + \sigma^2 m_{j,n}$$

While this equation provides an exact solution, it is computationally expensive to calculate the product log function. Furthermore, when  $\hat{y}_{j,n} + \sigma^2 m_{j,n}$  is too large, it is not possible to compute  $e^{\hat{y}_{j,n} + \sigma^2 m_{j,n}}$  (out of range). We can use an approximation of the lambert function in such cases, using the equation  $W(e^{x+a}) \sim x \left(1 - \frac{\log x - a}{x+1}\right)$  which is a good approximation when  $x$  is large and  $a \ll x$ , but this procedure further increases the computational cost by requiring element-wise evaluation of  $\hat{y}_{j,n} + \sigma^2 m_{j,n}$ . Therefore, we use an alternative approach to approximate  $\mathbf{Y}$ , based on Halley's method, as described below.

Consider again the following equation:

$$\sigma^2 e^y + y - \hat{y}_{j,n} - \sigma^2 m_{j,n} = 0$$

We can use Halley's method to update  $y$  iteratively, using the equation:

$$y_{t+1} = y_t - \frac{2f(y_t)f'(y_t)}{2[f'(y_t)]^2 - f(y_t)f''(y_t)}$$

$$\begin{aligned} f(y) &= \sigma^2 e^y + y - \hat{y}_{j,n} - \sigma^2 m_{j,n} \\ f'(y) &= \sigma^2 e^y + 1 \\ f''(y) &= \sigma^2 e^y \end{aligned}$$

In practice, this iterative procedure quickly converges on the solution for  $y$ .

Note that calculating  $f$  and its derivatives requires the calculation of  $e^y$ . Since  $y$  is the logarithm of the expected read counts,  $e^y$  is expected to remain in a range that is feasible to compute. However, it is also possible to rearrange the iterative equation as below:

$$\begin{aligned} y_{t+1} &= y_t - \frac{2f(y_t)f'(y_t)}{2[f'(y_t)]^2 - f(y_t)f''(y_t)} \\ y_{t+1} &= y_t - \frac{2[e^{-y_t}f(y_t)][e^{-y_t}f'(y_t)]}{2[e^{-y_t}f'(y_t)]^2 - [e^{-y_t}f(y_t)][e^{-y_t}f''(y_t)]} \\ e^{-y_t}f(y_t) &= \sigma^2 + e^{-y_t}(y_t - \hat{y}_{j,n} - \sigma^2 m_{j,n}) \\ e^{-y_t}f'(y_t) &= \sigma^2 + e^{-y_t} \\ e^{-y_t}f''(y_t) &= \sigma^2 \end{aligned}$$

This provides the possibility of using the first set of equations when  $y$  is negative, and the second set when  $y$  is positive, in order to avoid calculation of the exponential of large positive numbers.

## Solving $\sigma^2$

The maximum likelihood solution for  $\sigma^2$  is:

$$\begin{aligned}
\arg \min_{\sigma^2} Q(\theta|\theta^{(t)}) &= \arg \min_{\sigma^2} \int \log P(\mathbf{Y}|\theta) P(\mathbf{Y}|\mathbf{M}, \theta^{(t)}) d\mathbf{Y} + \log P(\theta|\mathbf{C}, \mathbf{H}) = \\
&= \arg \min_{\sigma^2} \frac{NJ}{2} \log(2\pi\sigma^2) + \frac{1}{2\sigma^2} \sum_j \sum_n \text{Var}(y_{j,n}|\mathbf{M}, \theta^{(t)}) \\
&+ \frac{1}{2\sigma^2} \sum_j \sum_n [E(y_{j,n}|\mathbf{M}, \theta^{(t)}) - \hat{y}_{j,n}]^2 + \frac{J}{2} \log(\sigma^2) + \frac{1}{2\sigma^2 S_{\tilde{\theta}}} \|\tilde{\theta} - \tilde{\theta}_0\|_2^2 \\
&+ \sum_{i \in [1,n]} \left[ \frac{N_i}{2} \log(\sigma^2) + \frac{1}{2\sigma^2 S_{s,i}} \|\mathbf{s}_i - \mathbf{s}_{i,0}\|_2^2 \right] \\
&+ \sum_{i \in [1,n]} \left[ \frac{J}{2} \log(\sigma^2) + \frac{1}{2\sigma^2 S_{o,i}} \|\mathbf{o}_i\|_2^2 \right] \\
&+ \sum_{i \in [1,n]} \left[ \frac{K}{2} (J+L) \log(\sigma^2) + \frac{1}{2\sigma^2 S_{Q,i}} \|\mathbf{Q}_i - \mathbf{H}\mathbf{R}_i\|_2^2 + \frac{1}{2\sigma^2 S_{Q,i} S_{R,i}} \|\mathbf{R}_i\|_2^2 \right] \\
&+ \frac{K}{2} (J+P) \log(\sigma^2) + \frac{1}{2\sigma^2 S_Z} \|\mathbf{Z} - \mathbf{C}\mathbf{A}\|_2^2 + \frac{1}{2\sigma^2 S_Z S_A} \|\mathbf{A}\|_2^2
\end{aligned}$$

We can solve this minimization problem by setting the derivative of  $\sigma^2$  to zero, which leads to:

$$\begin{aligned}
&\frac{J(N+n) + N + J + nK(J+L) + K(J+P)}{2\sigma^2} \\
&= \frac{1}{2(\sigma^2)^2} \left[ \sum_j \sum_n \text{Var}(y_{j,n}|\mathbf{M}, \theta^{(t)}) + \sum_j \sum_n [E(y_{j,n}|\mathbf{M}, \theta^{(t)}) - \hat{y}_{j,n}]^2 \right. \\
&+ \sum_i \left( \frac{1}{S_{\tilde{\theta}}} \|\tilde{\theta} - \tilde{\theta}_0\|_2^2 + \frac{1}{S_{s,i}} \|\mathbf{s}_i - \mathbf{s}_{i,0}\|_2^2 + \frac{1}{S_{o,i}} \|\mathbf{o}_i\|_2^2 + \frac{1}{S_{Q,i}} \|\mathbf{Q}_i - \mathbf{H}\mathbf{R}_i\|_2^2 \right. \\
&\left. \left. + \frac{1}{S_{Q,i} S_{R,i}} \|\mathbf{R}_i\|_2^2 \right) + \frac{1}{S_Z} \|\mathbf{Z} - \mathbf{C}\mathbf{A}\|_2^2 + \frac{1}{S_Z S_A} \|\mathbf{A}\|_2^2 \right] \\
\sigma^2 &= \frac{1}{J(N+n) + N + J + nK(J+L) + K(J+P)} \left[ \sum_j \sum_n \text{Var}(y_{j,n}|\mathbf{M}, \theta^{(t)}) \right. \\
&+ \sum_j \sum_n [E(y_{j,n}|\mathbf{M}, \theta^{(t)}) - \hat{y}_{j,n}]^2 \\
&+ \sum_i \left( \frac{1}{S_{\tilde{\theta}}} \|\tilde{\theta} - \tilde{\theta}_0\|_2^2 + \frac{1}{S_{s,i}} \|\mathbf{s}_i - \mathbf{s}_{i,0}\|_2^2 + \frac{1}{S_{o,i}} \|\mathbf{o}_i\|_2^2 + \frac{1}{S_{Q,i}} \|\mathbf{Q}_i - \mathbf{H}\mathbf{R}_i\|_2^2 \right. \\
&\left. \left. + \frac{1}{S_{Q,i} S_{R,i}} \|\mathbf{R}_i\|_2^2 \right) + \frac{1}{S_Z} \|\mathbf{Z} - \mathbf{C}\mathbf{A}\|_2^2 + \frac{1}{S_Z S_A} \|\mathbf{A}\|_2^2 \right]
\end{aligned}$$

Note how the *law of total variance* (below) appears as part of this solution:

$$\begin{aligned}
\text{Var}(\mathbf{Y} - \hat{\mathbf{Y}}) &= E[\text{Var}(\mathbf{Y} - \hat{\mathbf{Y}}|\mathbf{M}, \theta^{(t)})] + \text{Var}[E(\mathbf{Y} - \hat{\mathbf{Y}}|\mathbf{M}, \theta^{(t)})] \\
&= \frac{1}{NJ} \sum_j \sum_n \text{Var}(y_{j,n} - \hat{y}_{j,n}|\mathbf{M}, \theta^{(t)}) + \frac{1}{NJ} \sum_j \sum_n [E(y_{j,n}|\mathbf{M}, \theta^{(t)}) - \hat{y}_{j,n}]^2 \\
&= \frac{1}{NJ} \sum_j \sum_n \text{Var}(y_{j,n}|\mathbf{M}, \theta^{(t)}) + \frac{1}{NJ} \sum_j \sum_n [E(y_{j,n}|\mathbf{M}, \theta^{(t)}) - \hat{y}_{j,n}]^2
\end{aligned}$$

Since we have already calculated  $E(y_{j,n}|\mathbf{M}, \theta^{(t)})$ , calculating the second part is trivial. To obtain the variance of each element of the latent variable  $y_{j,n}$  given the counts  $\mathbf{M}$  and the current model parameters, again we use the Laplace's approximation, where variance is estimated as the value of the second derivative of the  $h$  function at its mode:

$$\begin{aligned} g(y) &= e^{h(y)} = e^{ym_{j,n} - e^y - \frac{1}{2\sigma^2}(y - \hat{y}_{j,n})^2} \\ h(y) &= ym_{j,n} - e^y - \frac{1}{2\sigma^2}(y - \hat{y}_{j,n})^2 \\ h'(y) &= m_{j,n} - e^y - \frac{1}{\sigma^2}(y - \hat{y}_{j,n}) \\ h''(y) &= -e^y - \frac{1}{\sigma^2} \\ -\frac{1}{h''(y)} &= \frac{1}{e^y + \frac{1}{\sigma^2}} \end{aligned}$$

And since mode of the  $h$  function is the expected value of  $y$ , therefore:

$$\text{Var}(y_{j,n}|\mathbf{M}, \theta^{(t)}) = \frac{1}{e^{E(y_{j,n}|\mathbf{M}, \theta^{(t)})} + \frac{1}{\sigma_{(t)}^2}}$$

$$\text{Var}(\mathbf{Y} - \hat{\mathbf{Y}}) = \frac{1}{NJ} \sum_j \sum_n \frac{1}{e^{E(y_{j,n}|\mathbf{M}, \theta^{(t)})} + \frac{1}{\sigma_{(t)}^2}} + \frac{1}{NJ} \sum_j \sum_n [E(y_{j,n}|\mathbf{M}, \theta^{(t)}) - \hat{y}_{j,n}]^2$$

### **Extension of the model to log-ratio of two entities, directly based on the count data**

Consider an omics experiment (e.g. a scRNA-seq experiment) in which for every observation “unit”  $j$  (e.g. for every gene, or exon, etc.) in every “sample”  $n$  (e.g., in a tumour sample, or in a single cell, etc.), two types of counts are observed, which for the sake of generalizability we call the observed number of successes ( $s$ ) and observed number of failures ( $f$ ) (following the notations for a Bernoulli trial). For example, if we are interested in mRNA splicing (and therefore measurement of exon inclusion levels),  $k_{s,j,n}$  would be the number of observed transcripts in sample  $n$  that contain the exon  $j$ , and  $k_{f,j,n}$  would be the number of observed transcripts in sample  $n$  that do not contain the exon  $j$ . Therefore, our observations can be summarized in two  $J \times N$  matrices  $\mathbf{K}_s$  and  $\mathbf{K}_f$ , where  $J$  and  $N$  are the number of observation units and samples, respectively (similar to  $\mathbf{M}$ , which is a  $J \times N$  matrix of counts).

For each unit  $j$  in sample  $n$ , we assume that  $k_{s,j,n}$  and  $k_{f,j,n}$  follow a binomial distribution governed by the unobserved parameter  $p_{j,n}$ :

$$P(k_{s,j,n}, k_{f,j,n} | n = k_{s,j,n} + k_{f,j,n}, p = p_{j,n}) = \binom{k_{s,j,n} + k_{f,j,n}}{k_{s,j,n}} (p_{j,n})^{k_{s,j,n}} (1 - p_{j,n})^{k_{f,j,n}}$$

The interpretation of the parameter  $p_{n,j}$  depends on the context. For example, in the case of mRNA splicing,  $p_{j,n}$  would be equal to the percent-spliced-in (PSI) value for exon  $j$  in sample  $n$ .

For simplicity in what follows, instead of working directly with  $p_{j,n}$  (probability), we work with  $y_{j,n} = \text{logit}(p_{j,n}) = \log(p_{j,n}/(1-p_{j,n}))$ . Since the range of logit is  $-\infty$  to  $+\infty$ , it becomes easier to model it in the subsequent sections.

Our objective is to perform dimensionality reduction, imputation, and integration on the latent  $J \times N$  matrix  $\mathbf{Y}$ , given the observed matrices  $\mathbf{K}_s$  and  $\mathbf{K}_f$ .

### Model formulation

Similar to the previous sections, let's assume that we have the set of current GEDI model parameters  $\theta$ , so that:

$$\begin{aligned}\hat{\mathbf{Y}}_i &= \tilde{\mathbf{o}}^T \mathbf{j}_i + \mathbf{o}_i^T \mathbf{j}_i + \mathbf{j}'^T \mathbf{s}_i + (\mathbf{Q}_i + \mathbf{Z}) \mathbf{D} \mathbf{B}_i \\ \hat{\mathbf{Y}} &= [\hat{\mathbf{Y}}_1 \quad \dots \quad \hat{\mathbf{Y}}_n] \\ \mathbf{Y} &\sim N(\hat{\mathbf{Y}}, \sigma^2 \mathbf{I})\end{aligned}$$

Here,  $\hat{\mathbf{Y}}$  is the current prediction of  $\mathbf{Y}$  by the GEDI model.

Furthermore, from the assumption of binomial distribution, we have:

$$\mathbf{K}_s | \mathbf{K}_s + \mathbf{K}_f, \mathbf{Y} \sim B\left(\mathbf{K}_s + \mathbf{K}_f, \mathbf{P} = \frac{1}{1 + e^{-\mathbf{Y}}}\right)$$

We are interested in estimating the model parameters  $\theta$ , given the observations  $\mathbf{K}_s$  and  $\mathbf{K}_f$ , by maximizing the likelihood. Similar to the previous section we can show that an EM approach leads to the requirement to calculate the conditional  $E(\mathbf{Y})$  in each iteration given the observations  $\mathbf{K}_s$  and  $\mathbf{K}_f$  and the current estimates of  $\hat{\mathbf{Y}}$  and  $\sigma^2$ , followed by finding the  $\theta$  that maximizes the likelihood given  $E(\mathbf{Y})$ .

The expected value of each element  $(j, n)$  of  $\mathbf{Y}$  (i.e. expression of the gene  $j$  in cell  $n$ ) is:

$$E(y_{j,n} | m_{j,n}, \hat{y}_{j,n}) = \int_{-\infty}^{+\infty} P(y | m_{j,n}, \hat{y}_{j,n}) y dy$$

where  $P(y | m_{j,n}, \hat{y}_{j,n})$  is the posterior probability of  $y$  given the counts  $k_{s,j,n}$  and  $k_{f,j,n}$  and the model parameters  $\theta^{(l)}$  at time  $t$ , with the effect of model parameters  $\theta^{(l)}$  summarized in  $\hat{y}_{j,n}$ . Therefore:

$$\begin{aligned}P(y | m_{j,n}, \hat{y}_{j,n}) &= \frac{P(y, m_{j,n}, \hat{y}_{j,n})}{P(m_{j,n}, \hat{y}_{j,n})} = \frac{P(m_{j,n} | y) P(y | \hat{y}_{j,n}) P(\hat{y}_{j,n})}{P(m_{j,n}, \hat{y}_{j,n})} \\ &= \frac{P(\hat{y}_{j,n})}{P(m_{j,n}, \hat{y}_{j,n})} \times \binom{k_{s,j,n} + k_{f,j,n}}{k_{s,j,n}} \left(\frac{1}{1 + e^{-y}}\right)^{k_{s,j,n}} \left(\frac{1}{1 + e^y}\right)^{k_{f,j,n}} \times \frac{e^{-\frac{1}{2\sigma^2}(y - \hat{y}_{j,n})^2}}{\sigma\sqrt{2\pi}}\end{aligned}$$

This leads to:



$$\begin{aligned}
E(y_{j,n}|m_{j,n}, \hat{y}_{j,n}) &= c \int_{-\infty}^{+\infty} \left( \frac{1}{1+e^{-y}} \right)^{k_{s,j,n}} \left( \frac{1}{1+e^y} \right)^{k_{f,j,n}} e^{-\frac{1}{2\sigma^2}(y-\hat{y}_{j,n})^2} y dy \\
&= c \int_{-\infty}^{+\infty} (1+e^{-y})^{-k_{s,j,n}} (1+e^y)^{-k_{f,j,n}} e^{-\frac{1}{2\sigma^2}(y-\hat{y}_{j,n})^2} y dy \\
&= c \int_{-\infty}^{+\infty} \left( \frac{1+e^y}{e^y} \right)^{-k_{s,j,n}} (1+e^y)^{-k_{f,j,n}} e^{-\frac{1}{2\sigma^2}(y-\hat{y}_{j,n})^2} y dy \\
&= c \int_{-\infty}^{+\infty} (e^y)^{k_{s,j,n}} (1+e^y)^{-(k_{s,j,n}+k_{f,j,n})} e^{-\frac{1}{2\sigma^2}(y-\hat{y}_{j,n})^2} y dy
\end{aligned}$$

where  $c$  is a normalizing factor.

We use Laplace's method to approximate this integral (in Laplace's method, the posterior mean is equal to posterior mode), which leads to:

$$E(y_{j,n}|m_{j,n}, \hat{y}_{j,n}) = \arg \max_y \left\{ k_{s,j,n} y - (k_{s,j,n} + k_{f,j,n}) \ln(1 + e^y) - \frac{1}{2\sigma^2} (y - \hat{y}_{j,n})^2 \right\}$$

For simplicity, from this point we are omitting the  $j,n$  subscript.

This maximization problem is convex, since the second derivative is negative:

$$\frac{d^2}{dy^2} \left[ k_s y - (k_s + k_f) \ln(1 + e^y) - \frac{1}{2\sigma^2} (y - \hat{y})^2 \right] = -\frac{(k_s + k_f)e^y}{(1 + e^y)^2} - \frac{1}{\sigma^2} < 0$$

To solve  $E(Y)$ , we set the derivative of the above  $LL$  function to zero:

$$\begin{aligned}
\frac{d}{dy} \left[ k_s y - (k_s + k_f) \ln(1 + e^y) - \frac{1}{2\sigma^2} (y - \hat{y})^2 \right] &= 0 \\
\Rightarrow k_s - \frac{(k_s + k_f)}{1 + e^{-y}} - \frac{y - \hat{y}}{\sigma^2} &= 0 \\
\Rightarrow \sigma^2 \frac{(k_s + k_f)}{1 + e^{-y}} - \sigma^2 k_s + y - \hat{y} &= 0 \\
\Rightarrow \sigma^2 (k_s + k_f) - \sigma^2 k_s (1 + e^{-y}) + y(1 + e^{-y}) - \hat{y}(1 + e^{-y}) &= 0 \\
\Rightarrow \sigma^2 (k_s + k_f) - \sigma^2 k_s - \sigma^2 k_s e^{-y} + y + y e^{-y} - \hat{y} - \hat{y} e^{-y} &= 0 \\
\Rightarrow \sigma^2 k_f - \hat{y} + y + (y - \hat{y} - \sigma^2 k_s) e^{-y} &= 0 \\
\Rightarrow y = W[(\hat{y} - y + \sigma^2 k_s) e^{\sigma^2 k_f - \hat{y}}] - \sigma^2 k_f + \hat{y}
\end{aligned}$$

In other words, if we define  $g(y) = W[(\hat{y} - y + \sigma^2 k_s) e^{\sigma^2 k_f - \hat{y}}] - \sigma^2 k_f + \hat{y}$ , then the solution is  $y_0$  such that  $y_0 = g(y_0)$ . This suggests a fixed-point iteration procedure for solving  $y$ , where in each iteration the current estimate of  $y$  is used in the right side of the equation above to obtain an updated  $y$ .

If we set  $y = \sigma^2 k_s + \hat{y}$ , then we have:

$$g(y) = W(0) - \sigma^2 k_f + \hat{y} = \hat{y} - \sigma^2 k_f$$

Note that  $\hat{y} - \sigma^2 k_f \leq \hat{y} + \sigma^2 k_s$ , and  $g(y)$  is a monotonically decreasing function. This suggests that solution must be located between  $\hat{y} - \sigma^2 k_f$  and  $\hat{y} + \sigma^2 k_s$ , as schematically shown with the following diagram:

<add diagram here>

Therefore, we obtain the following boundaries for the solution:

$$\hat{y} - \sigma^2 k_f \leq y_0 \leq \hat{y} + \sigma^2 k_s$$

Note that the fixed-point iteration does not converge for  $g(y)$ , since  $g(y)$  does not satisfy Lipschitz constant  $L < 1$ , but the boundaries obtained above help with the solution proposed below.

### *Optimization using Halley's method*

Let's start again from the first derivative of the  $-LL$  function:

$$f(y) = \sigma^2 k_f - \hat{y} + y + (y - \hat{y} - \sigma^2 k_s)e^{-y} = 0$$

Let's define  $\alpha = \hat{y} - \sigma^2 k_f$  and  $\beta = \hat{y} + \sigma^2 k_s$  (these are in fact the lower and upper boundaries obtained above, respectively). Then we have:

$$\begin{aligned} f(y) &= y - \alpha + (y - \beta)e^{-y} \\ f'(y) &= \frac{d}{dy}f(y) = 1 + e^{-y}(\beta - y + 1) \\ f''(y) &= \frac{d}{dy}f'(y) = e^{-y}(y - \beta - 2) \end{aligned}$$

These can be used to iteratively obtain better estimates of  $y$  as:

$$y_{t+1} = y_t - \frac{2f(y_t)f'(y_t)}{2[f'(y_t)]^2 - f(y_t)f''(y_t)}$$

It is easy to show that within the solution boundaries identified in the previous section, the first derivative of  $f(y)$  is always positive, and the second derivative is always negative. This creates a well behaving curve within these boundaries that results in convergence using either the Halley's method (above) or Newton's method.

Note that when  $-y$  is large, the solution above requires computation of  $e^{-y}$ , which can result in numerical instability or out of range results. We can instead use the following calculations:

$$y_{t+1} = y_t - \frac{2[e^{y_t}f(y_t)][e^{y_t}f'(y_t)]}{2[e^{y_t}f'(y_t)]^2 - [e^{y_t}f(y_t)][e^{y_t}f''(y_t)]}$$

$$\begin{aligned} e^{y_t}f(y_t) &= e^{y_t}(y_t - \alpha) + y_{nt} - \beta \\ e^{y_t}f'(y_t) &= e^{y_t} + \beta - y_t + 1 \\ e^{y_t}f''(y_t) &= y_t - \beta - 2 \end{aligned}$$

In practice, we use the first equation when  $y_t$  is positive, and the second equation when  $y_t$  is negative.

## Solving $\sigma^2$

Similar to the previous section, we can use the *law of total variance* to obtain the variance of error:

$$\begin{aligned} \text{Var}(Y - \hat{Y}) &= E[\text{Var}(Y - \hat{Y} | \mathbf{K}_s, \mathbf{K}_f, \theta^{(t)})] + \text{Var}[E(Y - \hat{Y} | \mathbf{K}_s, \mathbf{K}_f, \theta^{(t)})] \\ &= \frac{1}{NJ} \sum_j \sum_n \text{Var}(y_{j,n} - \hat{y}_{j,n} | \mathbf{K}_s, \mathbf{K}_f, \theta^{(t)}) \\ &\quad + \frac{1}{NJ} \sum_j \sum_n [E(y_{j,n} | \mathbf{K}_s, \mathbf{K}_f, \theta^{(t)}) - \hat{y}_{j,n}]^2 \end{aligned}$$

To obtain the variance of each element of the latent variable  $y_{j,n}$  given the counts  $\mathbf{K}_s$  and  $\mathbf{K}_f$  and the current model parameters, again we use the Laplace's approximation, where variance is estimated as the value of the second derivative of the  $h$  function at its mode:

$$\begin{aligned} g(y) &= e^{h(y)} = (e^y)^{k_{s,j,n}} (1 + e^y)^{-(k_{s,j,n} + k_{f,j,n})} e^{-\frac{1}{2\sigma^2}(y - \hat{y}_{j,n})^2} \\ h(y) &= k_s y - (k_s + k_f) \ln(1 + e^y) - \frac{1}{2\sigma^2} (y - \hat{y})^2 \\ h'(y) &= k_s - \frac{(k_s + k_f)}{1 + e^{-y}} - \frac{y - \hat{y}}{\sigma^2} \\ h''(y) &= -\frac{(k_s + k_f)e^{-y}}{(1 + e^{-y})^2} - \frac{1}{\sigma^2} \\ -\frac{1}{h''(y)} &= \frac{1}{\frac{(k_s + k_f)e^{-y}}{(1 + e^{-y})^2} + \frac{1}{\sigma^2}} \end{aligned}$$

Note that for large negative values of  $y$ , the exponential in the equation below may become out of range. However, we have:

$$-\frac{1}{h''(y)} = \frac{1}{\frac{(k_s + k_f)e^{-y}}{(1 + e^{-y})^2} + \frac{1}{\sigma^2}} = \frac{1}{\frac{(k_s + k_f)e^{-y}e^{2y}}{(1 + e^{-y})^2 e^{2y}} + \frac{1}{\sigma^2}} = \frac{1}{\frac{(k_s + k_f)e^y}{(1 + e^y)^2} + \frac{1}{\sigma^2}}$$

Therefore, we can simply use the following equation to make sure we are always calculating the exponential of a negative value:

$$-\frac{1}{h''(y)} = \frac{1}{\frac{(k_s + k_f)e^{-|y|}}{(1 + e^{-|y|})^2} + \frac{1}{\sigma^2}}$$

And since mode of the  $h$  function is the expected value of  $y$ , therefore:

$$\text{Var}(y_{j,n} | \mathbf{K}_s, \mathbf{K}_f, \theta^{(t)}) = \frac{1}{\frac{(k_s + k_f)e^{-|E(y_{j,n} | \mathbf{K}_s, \mathbf{K}_f, \theta^{(t)})|}}{(1 + e^{-|E(y_{j,n} | \mathbf{K}_s, \mathbf{K}_f, \theta^{(t)})|})^2} + \frac{1}{\sigma_{(t)}^2}}$$

$$\begin{aligned}
Var(\mathbf{Y} - \hat{\mathbf{Y}}) &= \frac{1}{NJ} \sum_j \sum_n \frac{1}{\frac{(k_{s,j,n} + k_{f,j,n})e^{-|E(y_{j,n}|\mathbf{K}_s, \mathbf{K}_f, \theta^{(t)})|}}{(1 + e^{-|E(y_{j,n}|\mathbf{K}_s, \mathbf{K}_f, \theta^{(t)})|})^2} + \frac{1}{\sigma_{(t)}^2}} \\
&\quad + \frac{1}{NJ} \sum_j \sum_n [E(y_{j,n}|\mathbf{K}_s, \mathbf{K}_f, \theta^{(t)}) - \hat{y}_{j,n}]^2
\end{aligned}$$