Additional information for the paper

Melissa: Bayesian clustering and imputation of single cell methylomes

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1 Melissa: mean-field variational inference derivations

In mean-field variational inference the intractable posterior distribution of the latent variables

\[ p(\theta | \mathbf{X}) \]

is approximated by a factorized distribution

\[ q(\theta) = \prod_i q_i(\theta_i), \]

where \( \theta \) denotes the latent variables and \( \mathbf{X} \) the observed variables. Then we search over the space of approximating distributions to find the distribution with the minimum Kullback-Leibler (KL) divergence with the actual posterior

\[ \text{KL}(q(\theta) \mid| \mid p(\theta | \mathbf{X})) = - \int q(\theta) \ln \frac{p(\theta | \mathbf{X})}{q(\theta)} d\theta. \] (1)

The KL divergence can then be minimised by performing a free form minimisation over the \( q_i(\theta_i) \) leading to the following update equation

\[ q_i(\theta_i) = \frac{\exp \langle \ln p(\mathbf{X}, \theta) \rangle_{q_{j \neq i}}}{\int \exp \langle \ln p(\mathbf{X}, \theta) \rangle_{q_{j \neq i}} d\theta_i}, \] (2)

where \( \langle \cdot \rangle_{q_{j \neq i}} \) denotes an expectation with respect to the distributions \( q_j(\theta_j) \) for all \( j \neq i \). The joint distribution over the observed and latent variables for the Melissa model is

\[ p(\mathbf{Y}, \mathbf{Z}, \mathbf{C}, \mathbf{W}, \pi, \tau | \mathbf{X}) = p(\mathbf{Y}|\mathbf{Z}) p(\mathbf{Z}|\mathbf{C}, \mathbf{W}, \mathbf{X}) p(\mathbf{C}|\pi) p(\pi) p(\mathbf{W}|\tau) p(\tau), \] (3)

where the factorisation corresponds to the probabilistic graphical model shown in Figure 7 in the main text. We assume that the variational approximation to our posterior distribution factorises over the latent variables (mean-field variational inference)

\[ q(\mathbf{Z}, \mathbf{C}, \mathbf{W}, \pi, \tau) = q(\mathbf{Z}) q(\mathbf{C}) q(\mathbf{W}) q(\pi) q(\tau). \] (4)

1.1 Deriving optimised factors

Below we derive the optimised factors of the variational posterior using Equation (2).
Factor $q(C)$

$$
\ln q(C) = \langle \ln p(Y, Z, C, \pi, W, \tau | X) \rangle_{q(Z, \pi, W, \tau)} + \text{const}
$$

$$
= \left\langle \ln \left\{ \frac{p(Y | Z)}{p(Z | C, W, X)} \frac{p(Z | C, W, X)}{p(C | \pi)} \frac{p(C | \pi)}{p(\pi)} \frac{p(W | \tau)}{p(\tau)} \right\} \right\rangle_{q(Z, \pi, W, \tau)} + \text{const}
$$

$$
= \sum_{n=1}^{N} \sum_{k=1}^{K} c_{nk} \sum_{m=1}^{M} \langle \ln \mathcal{N}(z_{nm} | x_{nm} w_{mk}, I_{nm}) \rangle_{q(z_{nm}, w_{mk})} + \sum_{n=1}^{N} \sum_{k=1}^{K} \langle \ln \pi_k \rangle_{q(\pi_k)} + \text{const}
$$

$$
= \sum_{n=1}^{N} \sum_{k=1}^{K} c_{nk} \ln \rho_{nk} + \text{const},
$$

where

$$
\ln \rho_{nk} = \sum_{m=1}^{M} \left\langle -\frac{1}{2} (z_{nm} - x_{nm} w_{mk})^T \left( z_{nm} - x_{nm} w_{mk} \right) \right\rangle_{q(z_{nm}, w_{mk})} + \langle \ln \pi_k \rangle_{q(\pi_k)}.
$$

Taking the exponential on both sides and requiring that this distribution be normalised we obtain

$$
q(C) = \prod_{n=1}^{N} \prod_{k=1}^{K} r_{nk}^{c_{nk}}
$$

where

$$
r_{nk} = \frac{\rho_{nk}}{\sum_{j=1}^{K} \rho_{nj}}.
$$

Factor $q(\tau)$

$$
\ln q(\tau) = \left\langle \ln \left\{ \frac{p(Y | Z)}{p(Z | C, W, X)} \frac{p(Z | C, W, X)}{p(C | \pi)} \frac{p(C | \pi)}{p(\pi)} \frac{p(W | \tau)}{p(\tau)} \right\} \right\rangle_{q(Z, C, \pi, W)} + \text{const}
$$

$$
= \langle \ln p(W | \tau) \rangle_{q(W)} + \ln p(\tau) + \text{const}
$$

$$
= \sum_{k=1}^{K} \sum_{m=1}^{M} \langle \ln p(w_{mk} | \tau_k) \rangle_{q(w_{mk})} + \sum_{k=1}^{K} \ln p(\tau_k) + \text{const}.
$$

Here we observe that the right hand side comprises a sum over $k$, i.e. each $\tau_k$ is independent of each other, hence

$$
\ln q(\tau_k) = \sum_{m=1}^{M} \langle \ln p(w_{mk} | \tau_k) \rangle_{q(w_{mk})} + \ln p(\tau_k) + \text{const}
$$

$$
= \frac{MD}{2} \ln \tau_k - \frac{\tau_k}{2} \sum_{m=1}^{M} \left\langle w_{mk}^T w_{mk} \right\rangle_{q(w_{mk})} + (\alpha_0 - 1) \ln \tau_k - \beta_0 \tau_k
$$

$$
= (\alpha_k \text{ parameter}) \ln \tau_k - \left( \beta_k \text{ parameter} \right) \tau_k,
$$

which is the logarithm of the (un-normalised) Gamma distribution, leading to

$$
q(\tau_k) = \text{Gamma}(\tau_k | \alpha_k, \beta_k)
$$

$$
\alpha_k = \alpha_0 + \frac{MD}{2}
$$

$$
\beta_k = \beta_0 + \frac{1}{2} \sum_{m=1}^{M} \left\langle w_{mk}^T w_{mk} \right\rangle_{q(w_{mk})}.
$$
Note that the update for the $\alpha$ hyperparameter depends only on the total number of genomic regions and the number of basis functions used to estimate the underlying methylation profiles. On the other hand the $\beta$ hyperparameter is updated at each CAVI iteration, since it depends on the expected value of the regression coefficients. The expected value of the Gamma distribution is $E = \alpha / \beta$, and the inverse of this quantity is the variance parameter for the prior Gaussian distribution of the coefficients $w$. Large values of $E$ result in small variance Gaussian priors, hence the model is substantially penalised when weights are moving away from prior mean $\mu_0 = 0$; as a consequence the model will tend to prune away clusters, that is, set all weights $w_{mk} = 0$. This may strongly affect the model in the initial iterations of CAVI, which will affect the $\beta$ parameter but not the $\alpha$ parameter of the Gamma distribution, potentially leading to convergence to a suboptimal local maximum. Hence, one should be cautious when setting the initial values for these parameters; in the current implementation of Melissa we set $\alpha_0 = 0.5$ and $\beta_0 = \sqrt{\bar{a}_k}$.

Factor $q(\pi)$

$$\ln q(\pi) = \ln \left\{ \frac{p(Y|Z) p(Z|C, W, X) p(C|\pi) p(\pi) p(W|\tau) p(\tau)}{\text{const}} \right\} + \text{const}$$

$$= \ln p(\pi) + \langle \ln p(C|\pi) \rangle_{q(C)} + \text{const}$$

$$= \ln C(\delta_0) + \sum_{k=1}^{K} \ln \pi_k^{\delta_0-1} + \sum_{k=1}^{K} \sum_{n=1}^{N} \langle c_{nk} \rangle_{q(c_{nk})} \ln \pi_k + \text{const}$$

$$= \sum_{k=1}^{K} \ln \pi_k^{\delta_0-1} + \sum_{k=1}^{K} \sum_{n=1}^{N} r_{nk} \ln \pi_k + \text{const}. \quad (9)$$

Taking the exponential on both sides we observe that $q(\pi)$ is a Dirichlet distribution

$$q(\pi) = \prod_{k=1}^{K} \pi_k^{\delta_0 + \sum_{n=1}^{N} r_{nk} - 1}$$

$$= \text{Dir}(\pi|\delta). \quad (10)$$

where $\delta$ has components $\delta_k$ given by $\delta_k = \delta_0 + \sum_{n=1}^{N} r_{nk}$.

Factor $q(W)$

$$\ln q(w_{mk}) = \ln \left\{ \frac{p(Y|Z) p(Z|C, W, X) p(C|\pi) p(\pi) p(W|\tau) p(\tau)}{\text{const}} \right\} + \text{const}$$

$$= \sum_{n=1}^{N} \langle c_{nk} \rangle_{q(c_{nk})} \langle \ln N(z_{nm}|X_{nm}w_{mk}, I_{nm}) \rangle_{q(z_{nm})} + \langle \ln p(w_{mk}|\tau_k) \rangle_{q(\tau_k)} + \text{const}$$

$$= \sum_{n=1}^{N} r_{nk} \left\{ \frac{1}{2} (z_{nm} - X_{nm}w_{mk})^T (z_{nm} - X_{nm}w_{mk}) \right\}_{q(z_{nm})} - \frac{1}{2} \langle \tau_k \rangle_{q(\tau_k)} w_{mk}^T w_{mk} + \text{const}$$

$$= \sum_{n=1}^{N} r_{nk} \left\{ w_{mk}^T X_{nm}^T (z_{nm})_{q(z_{nm})} - \frac{1}{2} w_{mk}^T X_{nm}^T X_{nm} w_{mk} \right\} - \frac{1}{2} \langle \tau_k \rangle_{q(\tau_k)} w_{mk}^T w_{mk} + \text{const}$$

$$= w_{mk}^T \sum_{n=1}^{N} r_{nk} X_{nm}^T (z_{nm})_{q(z_{nm})} - \frac{1}{2} w_{mk}^T \left\{ \langle \tau_k \rangle_{q(\tau_k)} I + \sum_{n=1}^{N} r_{nk} X_{nm}^T X_{nm} \right\} w_{mk} + \text{const}. \quad (11)$$
We can derive the expectations in a similar fashion to Section 1.1. The ELBO

\[ \text{Factor } q(Z) \] The log of the optimised factor assuming that the corresponding \( y_{nmi} = 1 \) is

\[
\ln q(z_{nmi}) = \ln \left\{ \ln \left\{ p(Y|Z) p(Z|C, W, X) p(C|\pi) p(\pi) p(W|\tau) p(\tau) \right\}_\text{const} \right\}_{q(C, \pi, W, \tau)} + \text{const} \\
= \ln p(y_{nmi}|z_{nmi}) + \ln \left( \prod_{k=1}^{K} \mathcal{N}(z_{nmi}|w_{mk}^T x_{nmi}, 1)_{c_{mk}} \right)_{q(c_{n}, w_{nmi})} + \text{const} \\
= y_{nmi} \ln 1(z_{nmi} > 0) + (1 - y_{nmi}) \ln 1(z_{nmi} \leq 0) + 0, \text{ since } y_{nmi} = 1 \\
= \frac{1}{2} z_{nmi}^2 \sum_{k=1}^{K} r_{nk} + z_{nmi} \sum_{k=1}^{K} r_{nk} \langle w_{mk}^T q(w_{mk}) x_{nmi} \rangle + \text{const.}
\]

Exponentiating this quantity and setting \( \mu_{nmi} = \sum_{k=1}^{K} r_{nk} \langle w_{mk}^T q(w_{mk}) x_{nmi} \rangle \) we obtain

\[
q(z_{nmi}) \propto 1(z_{nmi} > 0) \exp \left( -\frac{1}{2} z_{nmi}^2 + z_{nmi} \mu_{nmi} \right).
\]

We observe that the optimized factor \( q(z_{nmi}) \) is an un-normalised Truncated Normal distribution

\[
q(z_{nmi}) = \begin{cases} 
\mathcal{T}\mathcal{N}_+ (z_{nmi}|\mu_{nmi}, 1) & \text{if } y_{nmi} = 1 \\
\mathcal{T}\mathcal{N}_- (z_{nmi}|\mu_{nmi}, 1) & \text{if } y_{nmi} = 0.
\end{cases}
\]

1.2 Variational lower bound

The variational lower bound \( \mathcal{L}(q) \) (i.e. evidence lower bound (ELBO)) is given by

\[
\mathcal{L}(q) = \sum_{C} \int \int \int \int q(Z, C, \pi, W, \tau) \ln \left\{ \frac{p(Y, Z, C, \pi, W, \tau|X)}{q(Z, C, \pi, W, \tau)} \right\} dZ d\pi dW d\tau \\
= \langle \ln p(Y|Z) \rangle_{q(Z)} + \langle \ln p(Z|C, W, X) \rangle_{q(Z, C, W, X)} + \langle \ln p(C|\pi) \rangle_{q(C, \pi)} + \langle \ln p(\pi) \rangle_{q(\pi)} \\
+ \langle \ln p(W|\tau) \rangle_{q(W, \tau)} + \langle \ln p(\tau) \rangle_{q(\tau)} - \langle \ln p(Y) \rangle_{q(Y)} - \langle \ln p(Z) \rangle_{q(Z)} - \langle \ln p(C) \rangle_{q(C)} \\
- \langle \ln q(\pi) \rangle_{q(\pi)} - \langle \ln q(W) \rangle_{q(W)} - \langle \ln q(\tau) \rangle_{q(\tau)}.
\]

We can derive the expectations in a similar fashion to Section 1.1. The ELBO \( \mathcal{L}(q) \) is used to assess convergence of the coordinate ascent variational inference (CAVI) algorithm (Blei et al., 2017).
1.3 Predictive density

The predictive density of a new observation $y_*$ which will be associated with a latent variable $c_*$, latent observation $z_*$ and covariates $X_*$ is given by

$$p(y_*|X_*, Y, X) = \sum_c \int p(y_*, c_*, z_*, \pi, W, \tau|X_*, Y, X) \, d\pi \, d\tau \, dW \, dz_*$$

$$= \sum_c \int p(y_*|z_*) p(z_*|c_*, W, X_*) p(c_*|\pi)p(\pi, W, \tau|Y, X) \, d\pi \, d\tau \, dW \, dz_*$$

$$\simeq \sum_{k=1}^K \frac{\delta_k}{\delta} \int p(y_*|z_*) \mathcal{N}(z_*|X_*\lambda_k, I_n + \text{diag}(X_*S_kX_*^T)) \, dz_*$$

$$= \sum_{k=1}^K \frac{\delta_k}{\delta} \left\{ \int_0^\infty \mathcal{N}(z_*|X_*\lambda_k, I_n + \text{diag}(X_*S_kX_*^T)) \, dz \quad \text{where } y_* = 1 \right. \quad \left. \int_{-\infty}^0 \mathcal{N}(z_*|X_*\lambda_k, I_n + \text{diag}(X_*S_kX_*^T)) \, dz \quad \text{where } y_* = 0 \right\}$$

$$= \sum_{k=1}^K \frac{\delta_k}{\delta} \Phi(\rho)^{y_*} (1 - \Phi(\rho))^{(1-y_*)}$$

$$= \sum_{k=1}^K \frac{\delta_k}{\delta} \text{Bern}(y_*|\Phi(\rho))$$.

where $\delta = \sum_k \delta_k$, $\Phi(\cdot)$ denotes the cumulative distribution function (cdf) of the standard normal distribution and

$$\rho = \frac{X_*\lambda_k}{(I_n + \text{diag}(X_*S_kX_*^T))^{1/2}}.$$
Figure S1: Melissa robustly imputes CpG methylation states. (a) Imputation performance in terms of F-measure as we vary the proportion of covered CpGs used for training. Higher values correspond to better imputation performance. For each CpG coverage setting a total of 10 random splits of the data to training and test sets was performed. Each coloured circle corresponds to a different simulation. The plot shows also the LOESS curve for each method as we increase CpG coverage. (b) Imputation performance measured by F-measure for varying number of cells assayed. In (a) N = 200 cells were simulated and cluster dissimilarity was set to 0.5, and in (b) CpG coverage was set to 0.4 and cluster dissimilarity to 0.5.

Figure S2: Melissa robustly imputes CpG methylation states for different levels of dissimilarity across clusters; values closer to zero correspond to highly similar cell sub-populations, whereas values closer to one correspond to well separated cell sub-populations. Imputation performance is measured in terms of (a) AUC and (b) F-measure. Higher values correspond to better imputation performance. For each CpG coverage setting a total of 10 random splits of the data to training and test sets was performed. Each coloured circle corresponds to a different simulation. The plot shows also the LOESS curve for each method as we increase the cluster dissimilarity across cell sub-populations. The CpG coverage was set to 0.4 and a total of N = 200 cells were simulated per experiment.
Figure S3: Melissa efficiently imputes and clusters cell sub-populations. Running times for varying number of cells for the variational Bayes (VB) and Gibbs sampling implementations for the Melissa model, where each cell consists of $M = 200$ genomic regions.

Figure S4: Melissa robustly imputes CpG methylation states on the subsampled ENCODE RRBS methylation data. Imputation performance in terms of (a) AUC and (b) F-measure for varying levels of CpG coverage for pre-defined ±2.5 kb regions around TSS. For each CpG coverage setting a total of 10 random splits of the data to training and test sets was performed. Each dot corresponds to a different simulation.
Figure S5: Melissa robustly imputes CpG methylation states on the subsampled ENCODE WGBS methylation data. Imputation performance in terms of (a) AUC and (b) F-measure for varying levels of CpG coverage for pre-defined ±2.5 kb regions around TSS. For each CpG coverage setting a total of 10 random splits of the data to training and test sets was performed. Each dot corresponds to a different simulation.

Figure S6: (a) Precision recall curves and (b) receiver operating characteristic curves on varying CpG coverage levels for imputing CpG methylation states for the subsampled ENCODE RRBS methylation data for pre-defined ±2.5 kb regions around TSS.
**Figure S7:** (a) Precision recall curves and (b) receiver operating characteristic curves on varying CpG coverage levels for imputing CpG methylation states for the subsampled ENCODE WGBS methylation data for pre-defined ±2.5 kb regions around TSS.

**Figure S8:** Melissa robustly imputes CpG methylation states on the subsampled ENCODE RRBS methylation data. Imputation performance in terms of (a) AUC and (b) F-measure for varying levels of CpG coverage for pre-defined ±5 kb regions around TSS. For each CpG coverage setting a total of 10 random splits of the data to training and test sets was performed. Each dot corresponds to a different simulation.
Figure S9: Melissa robustly imputes CpG methylation states on the subsampled ENCODE WGBS methylation data. Imputation performance in terms of (a) AUC and (b) F-measure for varying levels of CpG coverage for pre-defined ±5 kb regions around TSS. For each CpG coverage setting a total of 10 random splits of the data to training and test sets was performed. Each dot corresponds to a different simulation.

Figure S10: Prediction performance using the F-measure metric for imputing CpG methylation states of the Angermueller et al. (2016) dataset. Higher values correspond to better imputation performance. Each coloured boxplot indicates the performance using 10 random splits of the data in training and test sets; due to high computational costs, DeepCpG was trained only once and the boxplots denote the variability across ten random subsamplings of the test set. Shown is the prediction performance for alternative genomic contexts: promoters (±1.5 kb, ±2.5 kb and ±5 kb regions), active enhancers, super enhancers and Nanog regulatory regions.
Figure S11: Receiver operating characteristic curves for imputing CpG methylation states of the Angermueller et al. (2016) dataset.

Figure S12: Precision recall curves for imputing CpG methylation states of the Angermueller et al. (2016) dataset.
Figure S13: Example profiles for different promoter regions of developmental genes with window length ±5kb for the Angermueller et al. (2016) dataset. Melissa identified three cell sub-populations.

Figure S14: Prediction performance using the F-measure metric for imputing CpG methylation states of the Smallwood et al. (2014) dataset. Higher values correspond to better imputation performance. Each coloured boxplot indicates the performance using 10 random splits of the data in training and test sets; due to high computational costs, DeepCpG was trained only once and the boxplots denote the variability across ten random subsamplings of the test set. Shown is the prediction performance for alternative genomic contexts: promoters (±1.5 kb, ±2.5 kb and ±5 kb regions), active enhancers, super enhancers and Nanog regulatory regions.
Figure S15: Receiver operating characteristic curves for imputing CpG methylation states of the Smallwood et al. (2014) dataset.

Figure S16: Precision recall curves for imputing CpG methylation states of the Smallwood et al. (2014) dataset.
Figure S17: Example profiles for different promoter regions with window length ± 5 kb for the Smallwood et al. (2014) dataset. Melissa identified three cell sub-populations.

Figure S18: Example profiles for different enhancer regions for the Smallwood et al. (2014) dataset. Melissa identified three cell sub-populations.

Figure S19: Digital output of single cell DNA methylation. Histogram of the distribution of CpG methylation values for 10 randomly sampled single cells from the Angermueller et al. (2016) study. As expected, the proportion of binary CpGs is very high (around 98.8%) and only around 0.5% of CpG sites are hemi-methylated.
Figure S20: Boxplots of CpG coverage distribution across different genomic contexts for the Angermueller et al. (2016) dataset after the filtering process. The x-axis shows CpG coverage bins and the y-axis shows the distribution of the number of genomic regions with N CpGs covered across cells, that is, each dot in the boxplot represents a different cell.

Figure S21: Boxplots of CpG coverage distribution across different genomic contexts for the Smallwood et al. (2014) dataset after the filtering process. The x-axis shows CpG coverage bins and the y-axis shows the distribution of the number of genomic regions with N CpGs covered across cells, that is, each dot in the boxplot represents a different cell.
### 3 Additional tables

<table>
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<th>Genomic context</th>
<th>CpGs (in millions)</th>
<th>Time (in hours)</th>
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<td>Active enhancers</td>
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Table S1: Melissa training time for the Angermueller et al. (2016) mouse ESC dataset. Across different genomic contexts are shown the total number of CpGs used for training set and the time required (in hours) for running Melissa to impute and cluster single cells. Note that the numbers in millions refer to the total number of CpGs not the genomic regions which are generally up to thousands. As a comparison, the DeepCpG model took about three to four days to train on around four million CpGs.

<table>
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<th>Genomic context</th>
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<td>Active enhancers</td>
<td>0.85</td>
<td>2</td>
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Table S2: Melissa training time for the Smallwood et al. (2014) mouse ESC dataset. Across different genomic contexts are shown the total number of CpGs used for training set and the time required (in hours) for running Melissa to impute and cluster single cells. Note that the numbers in millions refer to the total number of CpGs not the genomic regions which are generally up to thousands. As a comparison, the DeepCpG model took about three to four days to train on around four million CpGs.

<table>
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<th>Genomic context</th>
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<th>Angermueller study</th>
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<tr>
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Table S3: Sparsity level of the two scBS-seq data after filtering across different genomic regions.
References

