Cell-type specific analysis of heterogeneous methylation signal

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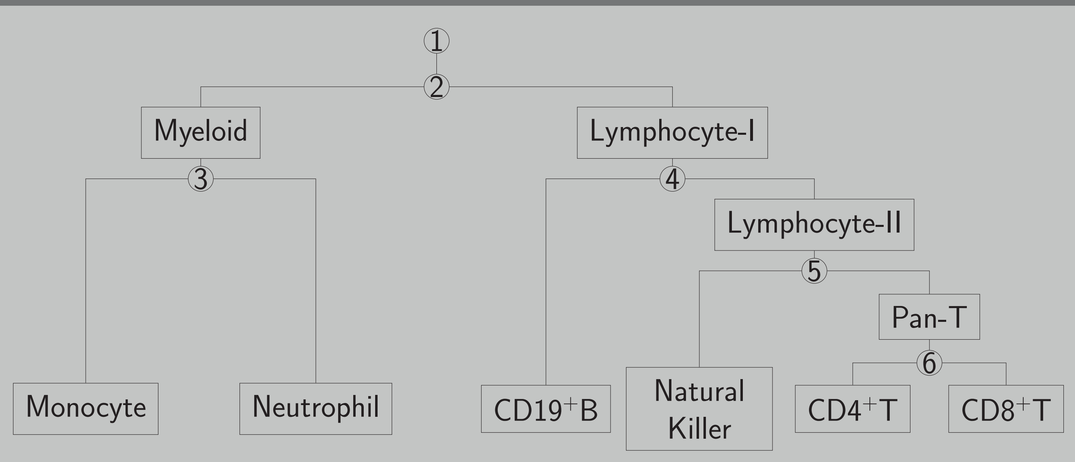
Figure: Haematopoeitic Lineage



Lineage Matrix:

$$\mathbf{A} = \begin{array}{c} \\ \text{Monocyte} \\ \text{Neutrophil} \\ \text{CD19}^{+}\text{B} \\ \text{Natural Killer} \\ \text{CD4}^{+}\text{T} \\ \text{CD8}^{+}\text{T} \end{array} \begin{array}{c} \begin{array}{cccccc} \textbf{Node:} & \textbf{1} & \textbf{2} & \textbf{3} & \textbf{4} & \textbf{5} \end{array} \\ \begin{pmatrix} 1 & -1/2 & -1/2 & 0 & 0 & 0 \\ 1 & -1/2 & +1/2 & 0 & 0 & 0 \\ 1 & +1/2 & 0 & -1/2 & 0 & 0 \\ 1 & +1/2 & 0 & +1/2 & -1/2 & 0 \\ 1 & +1/2 & 0 & +1/2 & +1/2 & -1/2 \\ 1 & +1/2 & 0 & +1/2 & +1/2 & +1/2 \end{pmatrix} \end{array}$$

Introduction

- Methylation arrays from blood are the most common type of epigenetic data collected, and are generally comprised of measurements from >100,000 genomic locations, called *loci*.
- When the methylation level at a locus is different between two sample groups, this is called *differential methylation*.
- Cell-type methylation levels vary, but are known to be related by the *haematopoeitic lineage*.
- Differential methylation can be cell-type-specific, where only a subset of blood cell-types in the sample are differentially methylated.
- **Objective**: Identify loci with differential methylation for *specific cell-types*

Model

Let y_i be the blood methylation level of sample i. Since y_i is constrained to the unit interval, a logit-Normal distribution was used.

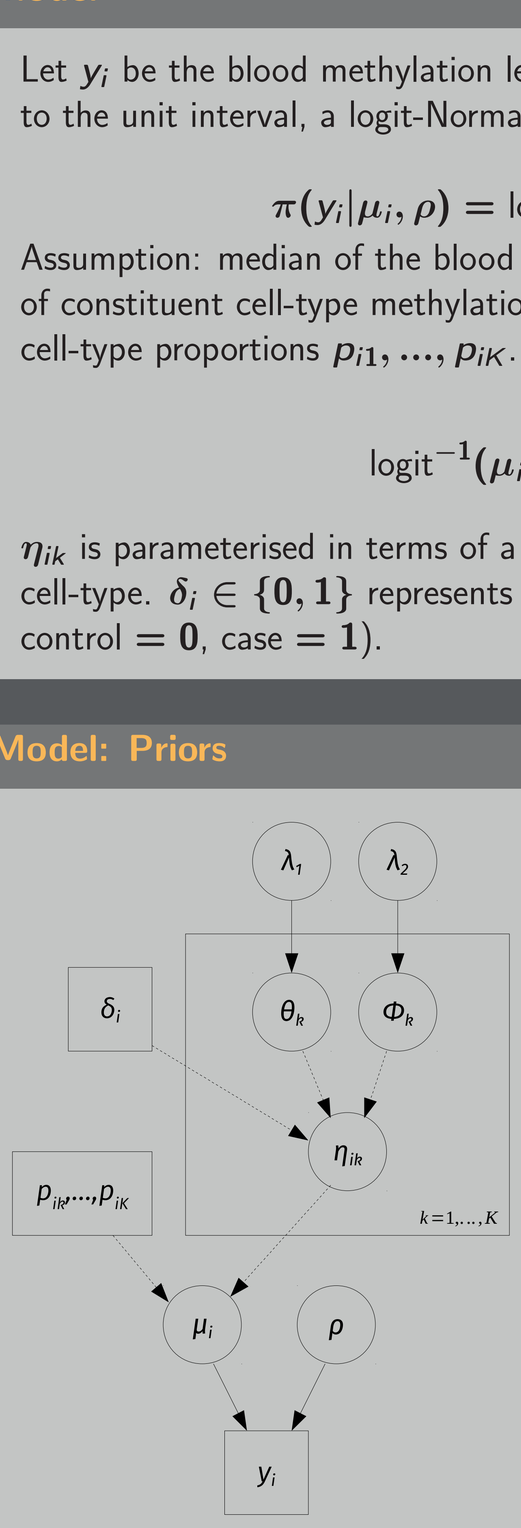
$$\pi(y_i|\mu_i, \rho) = \text{logitNormal}(y_i; \mu_i, \rho),$$

Assumption: median of the blood methylation level is a *linear combination* of constituent cell-type methylation levels $\eta_{i1}, ..., \eta_{iK}$, weighted by the cell-type proportions $p_{i1}, ..., p_{iK}$.

$$\text{logit}^{-1}(\mu_i) = \sum_{k=1}^{K} p_{ik}\eta_{ik}$$

η_{ik} is parameterised in terms of a baseline θ_k and a shift ϕ_k for each cell-type. $\delta_i \in \{0, 1\}$ represents the binary covariate of interest (e.g. control $= 0$, case $= 1$).

Model: Priors



Priors set on lineage-based contrasts:

$$\theta = \mathbf{A}\xi,$$
$$\phi = \mathbf{A}\zeta.$$

For $q \in \{2, ..., K\}$:

$$\pi(\xi_q|\lambda_1) = \text{Normal}\left(\xi_q; 0, \sqrt{\lambda_1}\right),$$
$$\pi(\zeta_q|\lambda_2) = \text{Normal}\left(\zeta_q; 0, \sqrt{\lambda_2}\right).$$

$$\pi(\lambda_1) = \text{Gamma}(\lambda_1; 1, \lambda_0),$$
$$\pi(\lambda_2) = \text{Gamma}(\lambda_2; 1, \lambda_0),$$
$$\pi(\rho) = \text{half-Cauchy}(\rho; 0, 5).$$

ξ_1 and ζ_1 are not cell-type related:

$$\pi(\xi_0) = \text{Cauchy}(\xi_0; 0, 10),$$
$$\pi(\zeta_0) = \text{Cauchy}(\zeta_0; 0, 10).$$

Method: Inference and Case Study

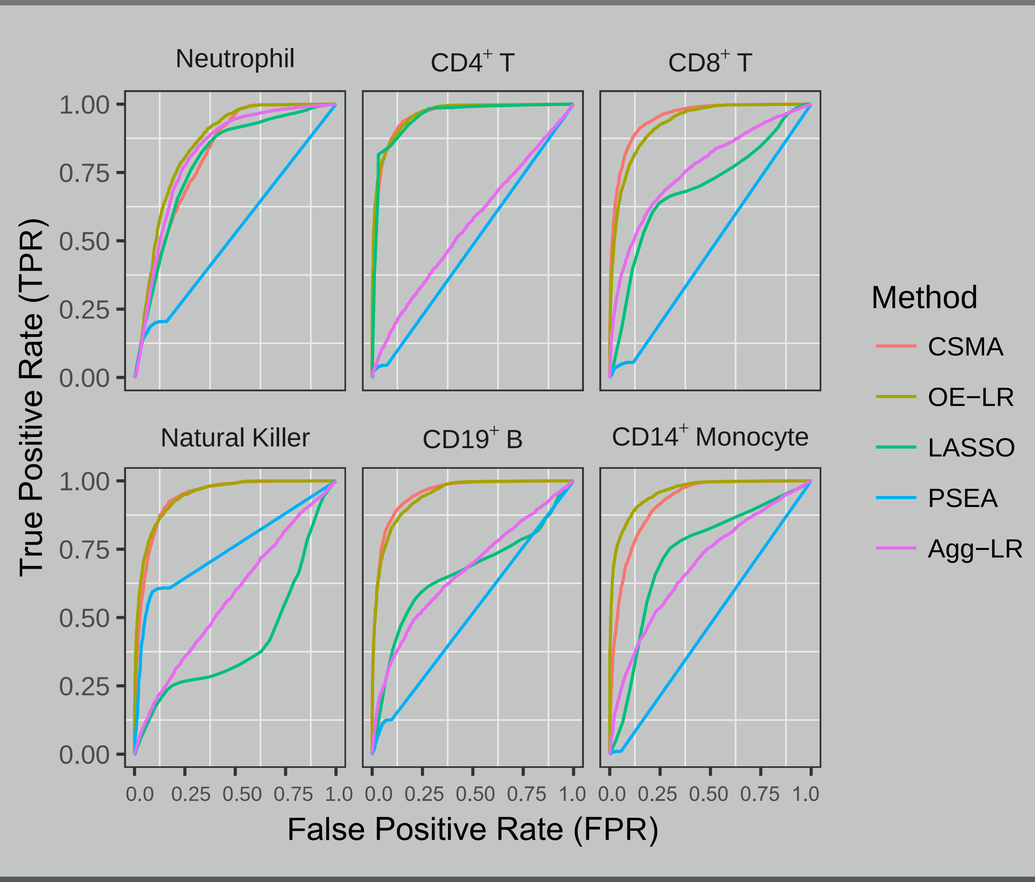
- Model fitted using numerical optimisation procedure in STAN [1].
- Obtained *Maximum A Posteriori* (MAP) estimates for ϕ parameters and a Hessian matrix estimate.
- Laplace approximations to the posterior calculated for each for ϕ_k.
- Predicted differential methylation for cell-type k if

$$\Pr\left(\left|\phi_k - \phi_k^{\text{MAP}}\right| > 0 | \text{Data}\right) < \alpha$$

Case study: find differentially methylated loci associated with sex.

- Data-set contained 5 females and 9 males.
- Cell-sorted data contained ground-truth for comparison with predictions.

Results



Results

- CSMA method outperformed other methods for CD8^{+}T and CD19^{+}B.
- OE-LR method outperformed CSMA for the Monocyte and Neutrophil cell-types.
- CSMA tended to detect more differentially methylated loci specific to the given cell-type.
- OE-LR tended to detect differentially methylated loci where all cell-types were differentially methylated.
- PSEA, Agg-LR, and LASSO methods were sub-optimal.

Conclusions

- CSMA and OE-LR are both useful for finding differentially methylated loci.
- Best method may be to use an *ensemble approach* for finding both cell-type specific and unspecific differentially methylated loci.

Current Work:

- Extending CSMA model to include multiple covariates and different data distributions.
- Reducing potential bias from inaccurate proportion estimates.
- Developing empirical Bayes approach for optimal value of λ_0.

References

[1] Stan Development Team.
RStan: the R interface to Stan, 2016.
R package version 2.14.1.

Acknowledgments

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