Factor regression for dimensionality reduction and data integration techniques with applications to cancer data

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Junior Bayes Beyond Borders (JB^3)

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Dr. Richard Savage
Pinpoint

Motivation

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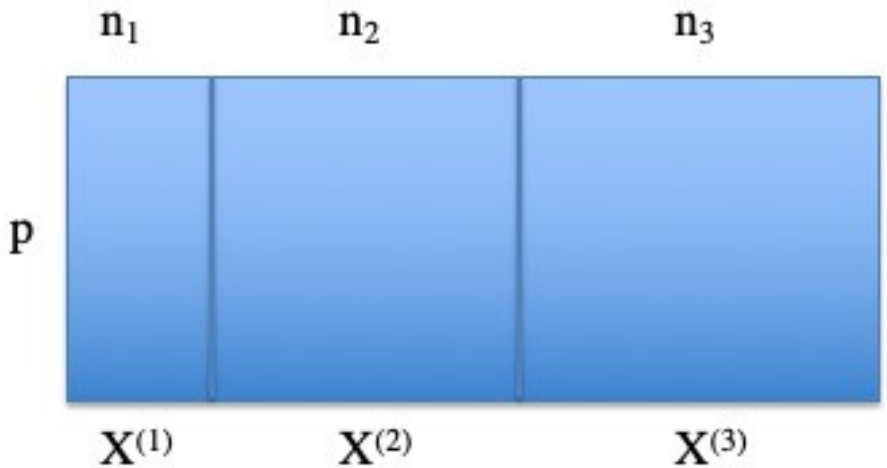
- **GOAL:** Combine multiple studies into a single analysis.



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2. A flexible Bayesian factor regression model to integrate large datasets, jointly learning batch and covariate effects and sparse low-rank covariances.
3. A novel and scalable non-local prior based formulation to induce sparsity and learn the number of factors. The first adaptation of non-local priors to factor models.

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3. A novel and scalable non-local prior based formulation to induce sparsity and learn the number of factors. The first adaptation of non-local priors to factor models.
4. A scalable EM algorithm with closed-form updates to obtain Mode a Posteriori (MAP) estimates and an R implementation publicly available `https://github.com/AleAviP/BFR.BE`.

Cancer statistics [1]

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CASES

18 million

New cases of cancer, worldwide, 2018.

DEATHS

9.6 million

Deaths from cancer, worldwide, 2018
1 in 6 deaths

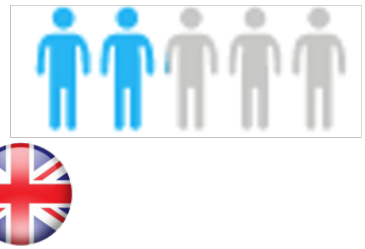
SURVIVAL

50%

Survive cancer for 10 or more years
UK, 2010-2011

PREVENTION

38%



Preventable cases 2015, UK

[1] https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-typ
https://www.who.int/news-room/fact-sheets/detail/cancer

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Large scale projects:

- The Cancer Genome Atlas (TCGA),
- Cancer Genome Project (CGP)
- International Cancer Genome Consortium (ICGC)

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Naïve approach

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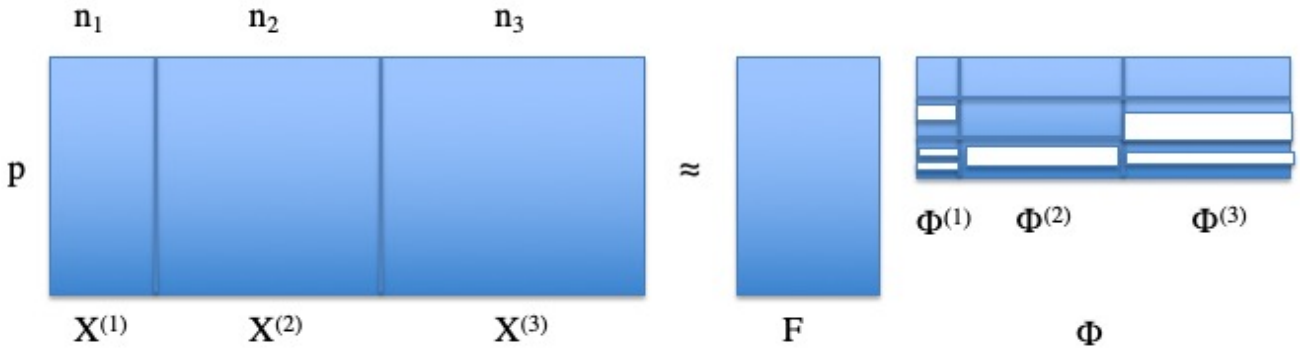
- Edefonti et al (2012) stack all the studies in **one** data-set: $\mathbf{x}_i^\top = \left((\mathbf{x}_i^{(1)})^\top, (\mathbf{x}_i^{(2)})^\top, \ldots, (\mathbf{x}_i^{(S)})^\top\right)$
- Perform factor analysis



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$$f_i \sim N(0, \mathbf{I})$$

$$\mathtt{e}_i \mid \mathcal{T} \sim N(0, \mathcal{T}^{-1})$$

$$\mathtt{x}_i \mid \mathtt{f}_i, \phi, \mathcal{T} \sim N(\phi f_i, \mathcal{T}^{-1})$$

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  - MLE, optimise: $\log \mathrm{p}(X|\phi, \mathcal{T})$
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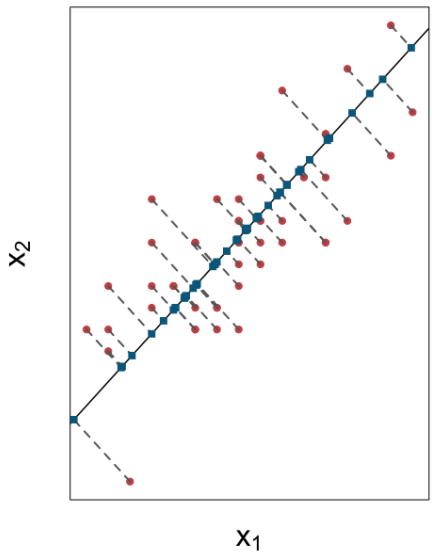

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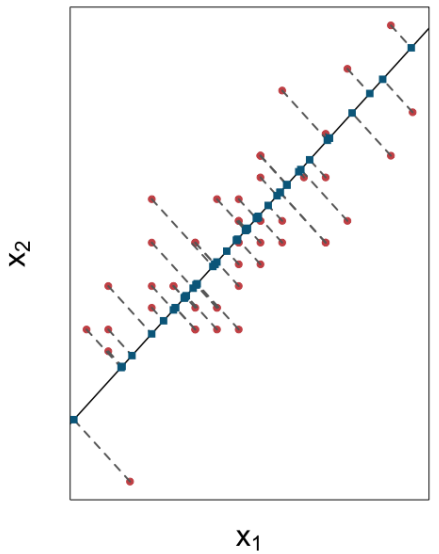

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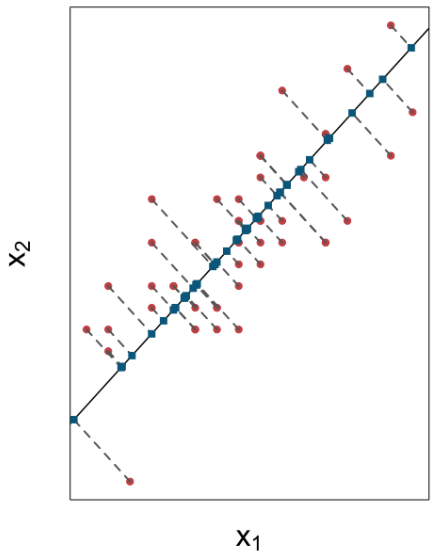

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  ϕ and $\mathcal{T}$ do not have a closed-form.
- When $\mathcal{T}^{-1} = \sigma_\epsilon^2 I$, we recover PPCA and PCA when $\mathcal{T}^{-1} = 0$.
- **Problem:** Provides limited flexibility to account for systematic biases or sources of variation that are not of interest

Batch effects

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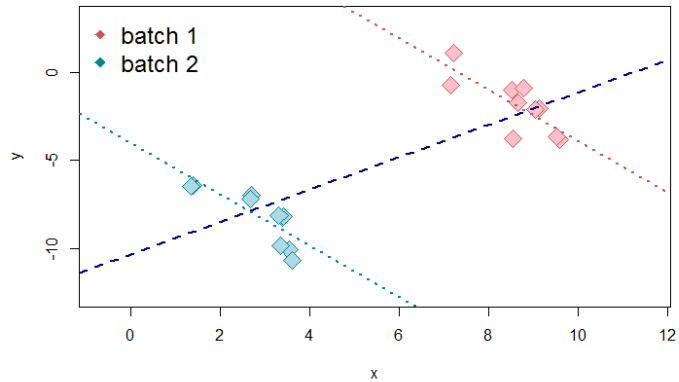

Ovarian cancer dataset

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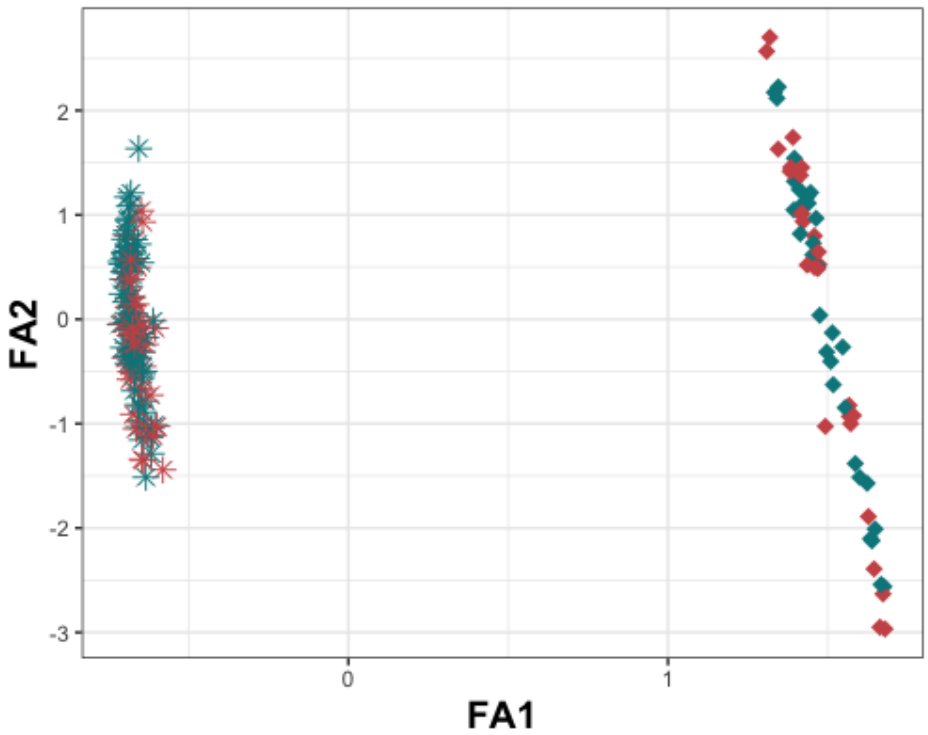

BFR with batch effect correction [2]

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Bayesian factor regression with batch effect correction:

- Model: $\mathtt{x}_i = \phi \mathtt{f}_i + \theta \mathtt{v}_i + \beta \mathtt{b}_i + \mathtt{e}_i$
  - $\theta \in \mathbb{R}^{p \times p_v}$: regression coefficients
  - $\beta \in \mathbb{R}^{p \times p_b}$: additive batch effects
  - $v_i \in \mathbb{R}^{p_v}$: observed covariates
  - $b_i \in \{0,1\}^{p_b}$: batch indicators
  - $\mathtt{e}_{ij} \sim N(0, \tau_{js}^{-1})$, τ_{js}: the j^{th} idiosyncratic precision element in batch s.

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- Priors
  - Idiosyncratic precisions: $\tau_{jl} \mid \eta, \xi \sim$ Gamma$(\eta/2, \eta\xi/2)$
  - Regression parameters: $(\theta_j, \beta_j) \sim N(0, \psi \mathbf{I})$

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- ✗ Dimension of latent factors needs to be specified.

Spike-and-slab prior on the loadings

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$$p(\phi_{jk} \mid \gamma, \lambda_0, \lambda_1) = (1 - \gamma_{jk})p(\phi_{jk} \mid \lambda_0, \gamma_{jk} = 0) + \gamma_{jk}p(\phi_{jk} \mid \lambda_1, \gamma_{jk} = 1)$$

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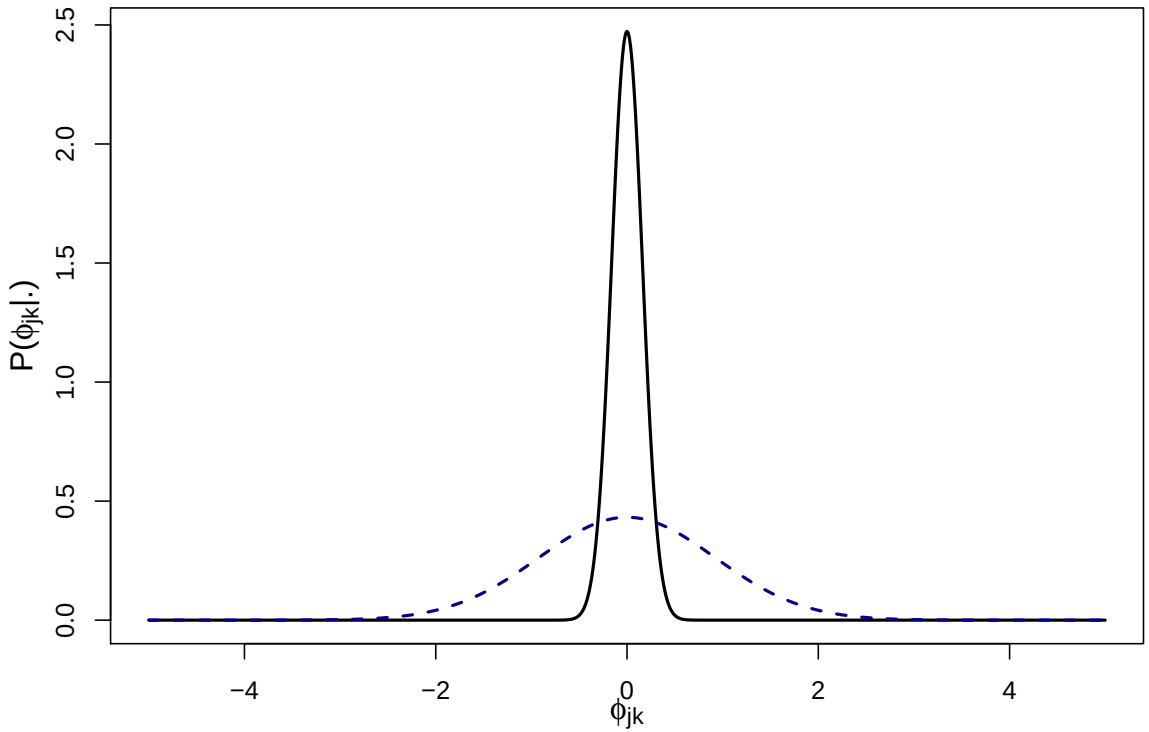

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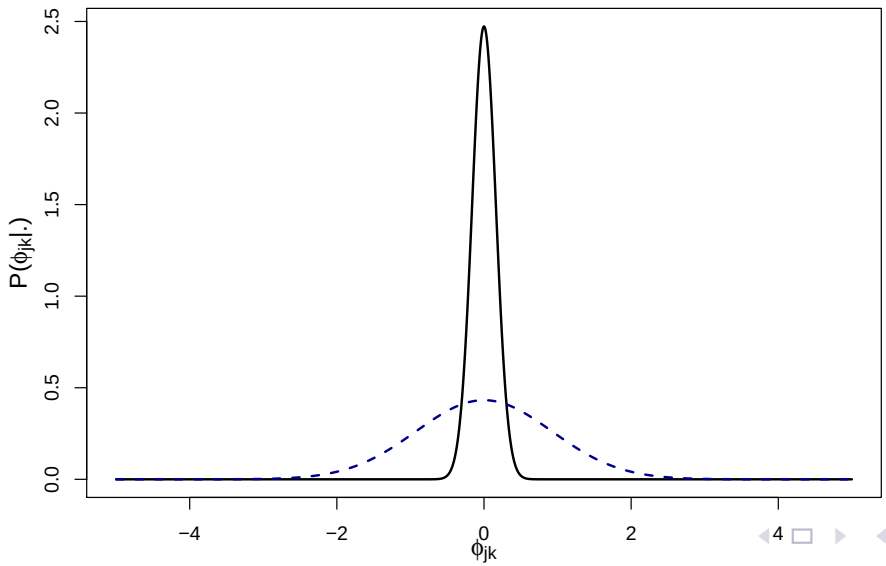
- ✗ Slab prior assigns non-negligible positive probability to regions consistent with null hypotheses.



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- ★ Normal-spike-and-MOM-slab [4]

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Non-local priors

An absolutely continuous measure with density $p(\phi_{jk} \mid \gamma_{jk} = 1)$ is a non-local prior if $\lim_{\phi_{jk} \to 0} p(\phi_{jk} \mid \gamma_{jk} = 1) = 0$.

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Novel non-local spike-and-slab priors

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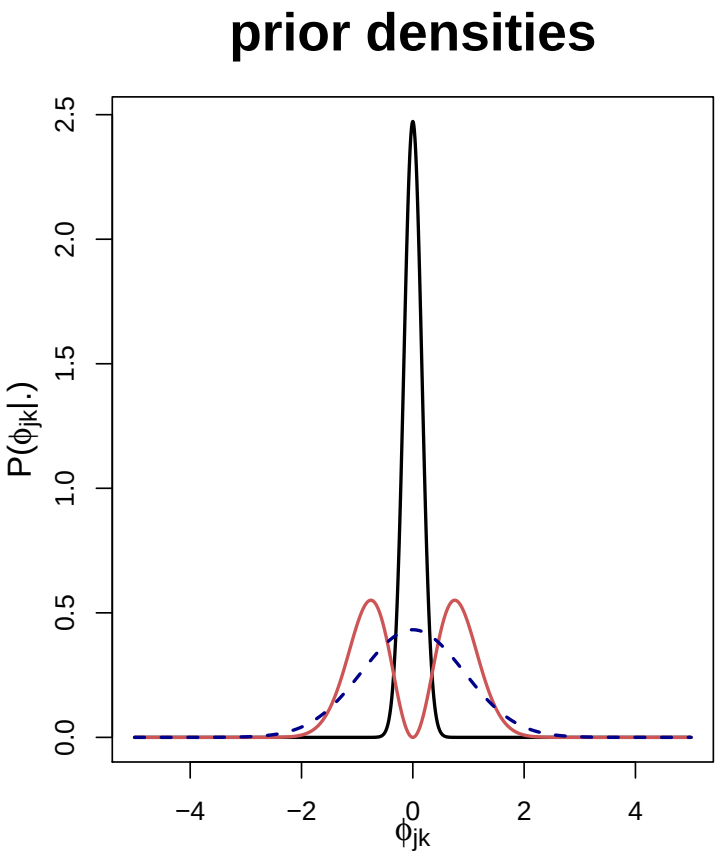

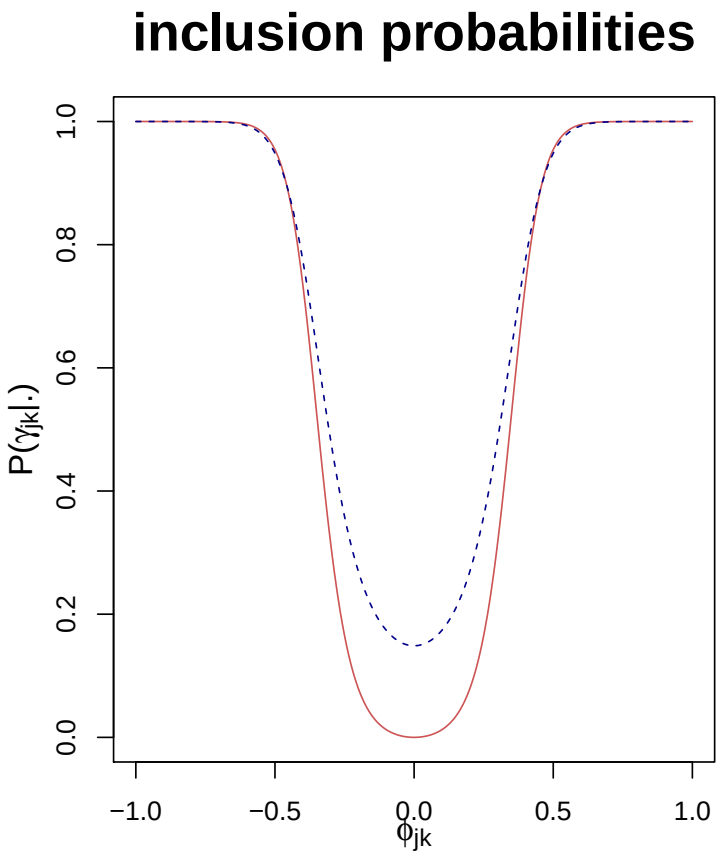

Hyper prior on the latent indicators

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Indian buffet process (IBP) prior [5]

$$\Gamma = \{\gamma_{jk}\}_{j,k=1}^{P,\infty}$$

[5] Griffiths and Ghahramani (2005) Technical report, Gatsby Computational Neuroscience Unit

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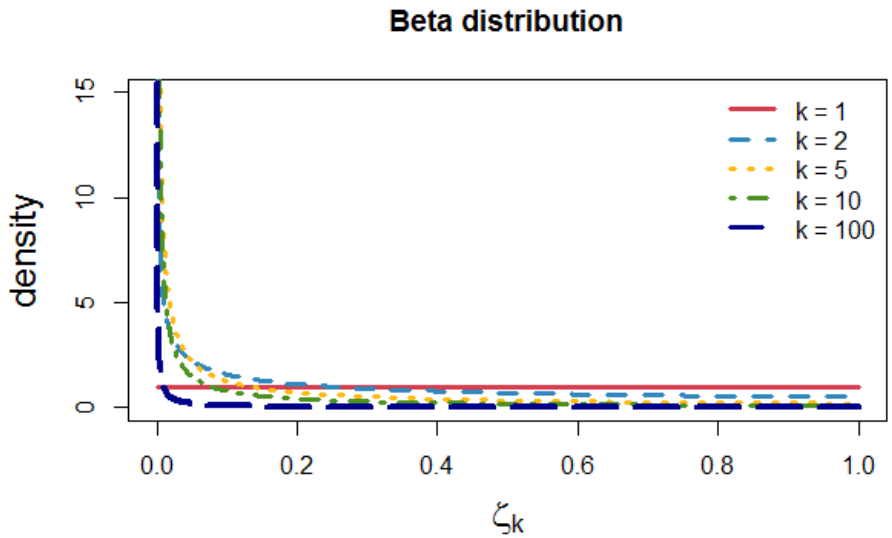

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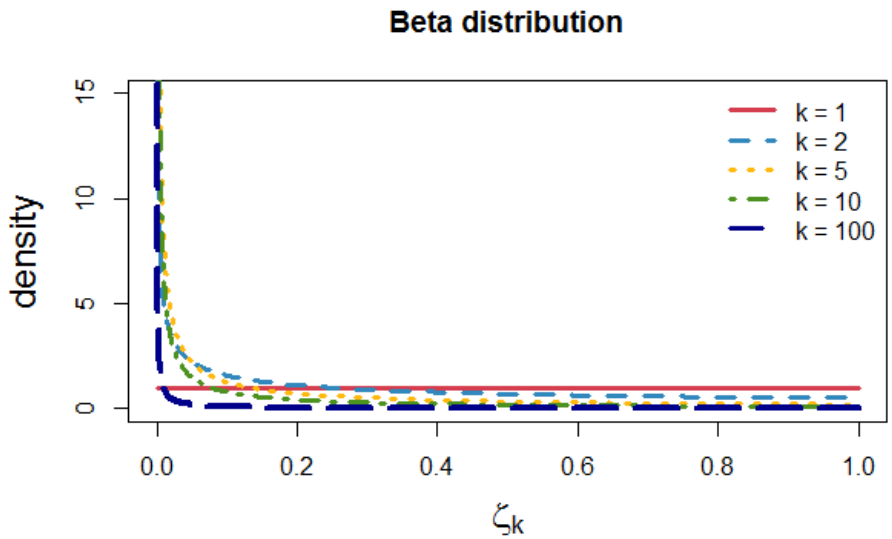

Inference is done via EM algorithm[6], providing closed-form expressions.

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Algorithm

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initialise $\hat{\phi} = \phi^{(0)}$, $\hat{\theta} = \theta^{(0)}$, $\hat{\beta} = \beta^{(0)}$, $\widehat{\mathcal{T}_{b_i}} = \mathcal{T}_{b_i}^{(0)}$, $\hat{\zeta} = \zeta^{(0)}$

while $\epsilon > \epsilon^*$, $\epsilon_\phi > \epsilon_\phi^*$ and $t < T$

E-step:

Latent factors: $\mathbb{E}[f_i|\hat{\Delta}, X] = (\mathbf{I}_q + \hat{\phi}^\top \widehat{\mathcal{T}_{b_i}} \hat{\phi})^{-1} \hat{\phi}^\top \widehat{\mathcal{T}_{b_i}} (x_i - \hat{\theta} v_i - \hat{\beta} b_i)$

Latent indicators$^+$*:* $\mathbb{E}[\gamma_{jk} \mid \hat{\Delta}] = \hat{p}_{jk}$

M-step:

Loadings$^+$*:* $\hat{\phi}_{jk} = arg\ max_{\phi_{jk}} Q_1(\hat{\Delta})$

Variances: $\hat{\tau}_l^{-1} = \frac{1}{n_l + \eta - 2} diag\left\{ \sum_{i:\ b_{il}=1} \left(\tilde{x}_i \tilde{x}_i^\top - 2\tilde{x}_i \mathbb{E}[f_i \mid \cdot]^\top \hat{\phi}^\top + \hat{\phi} \mathbb{E}[f_i f_i^\top \mid \cdot] \hat{\phi}^\top \right) + \eta \xi \mathbf{I}_p \right\}$

Coefficients: $(\hat{\theta}_j^\top, \hat{\beta}_j^\top) = \sum_i \left[\hat{\tau}_j^\top b_i (x_{ij} - \hat{\phi}_j^\top \mathbb{E}[f_i \mid \cdot])(v_i, b_i)^\top \right] \left[\sum_i \left[\hat{\tau}_j^\top b_i (v_i, b_i)(v_i, b_i)^\top \right] + \frac{1}{\psi} \mathbf{I} \right]^{-1}$

Weights: $\hat{\zeta}_k = \frac{\sum_{j=1}^p \hat{p}_{jk} + \frac{a_\zeta}{k} - 1}{\frac{a_\zeta}{k} + b_\zeta + p - 1}$

set $\Delta^{(t+1)} = \hat{\Delta}$ *and* $\phi^{(t+1)} = \hat{\phi}$

compute $\epsilon = Q(\Delta^{t+1}) - Q(\Delta^t)$, $\epsilon_\phi = \max ||\phi_{jk}^{(t+1)} - \phi_{jk}^{(t)}||$ *and* $t = t + 1$

end

Normal-spike-and-MoM-slab prior

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- ✓ Provides guidelines for the choice of λ_0 and λ_1

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- ✓ Corrects mean and variance batch effects.
- ✓ EM algorithm is able to effectively estimate and remove such biases.
- ✓ Dimension of the latent factors is learned
- ✓ Discriminates the important (slab), from the ignorable factors (spike).
- ✓ Provides guidelines for the choice of λ_0 and λ_1
- ✓ NLPs facilitate interpretation: well-separated hypotheses.

Normal-spike-and-MoM-slab prior

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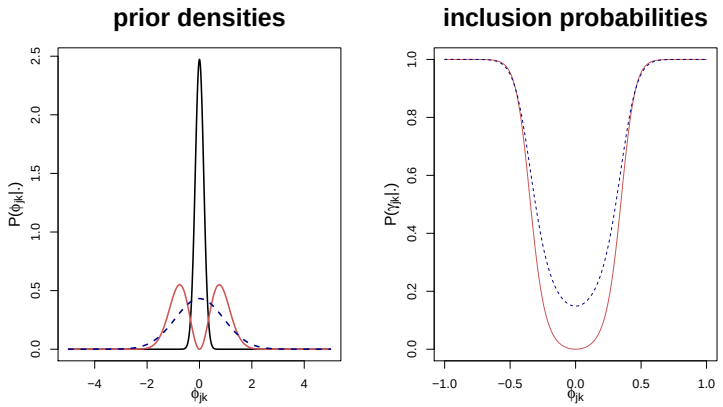
- ✓ Closed-form expressions of EM available (also approximations)



Laplace-spike-and-MoM-slab prior [7]

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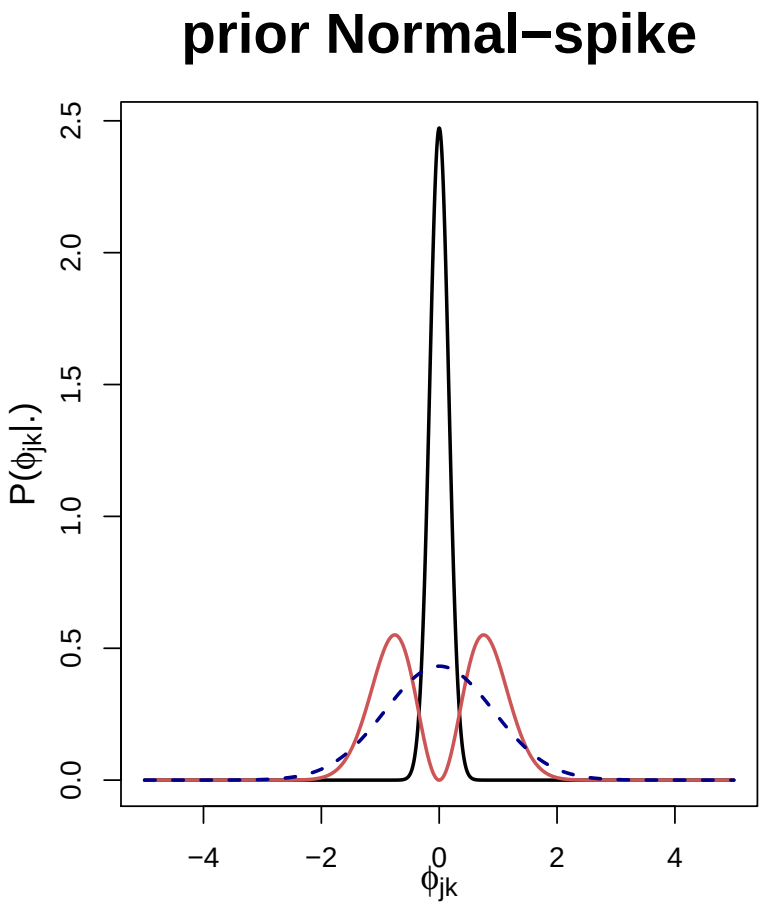
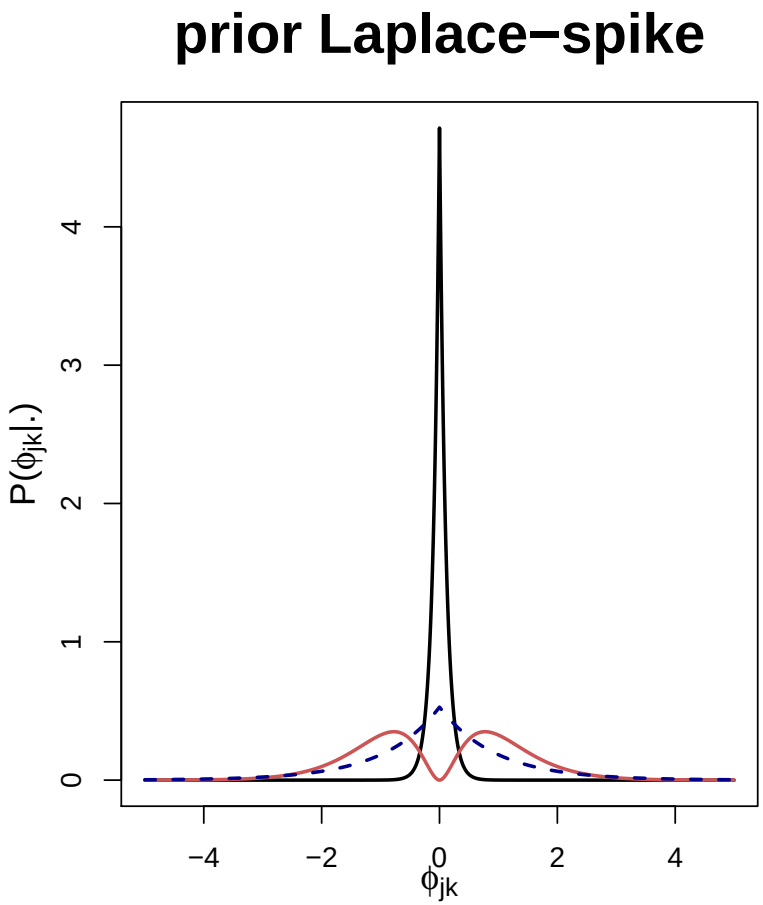




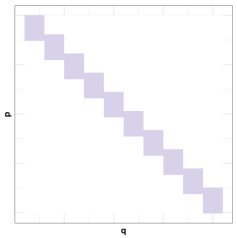
[7] Avalos-Pacheco A. , Rossell D. , Savage R. S. , (2020+) arXiv

Simulation studies

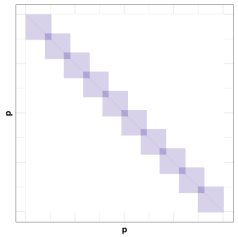
Harvard-MIT Center for Regulatory Science

Synthetic data **without** batch effects for $n = 100$, $q^* = 10$, $p = 1,000$ or $1,500$ parameters, truly sparse loadings ϕ^*.

ϕ



$\phi\phi^\top + \mathcal{T}^{-1}$



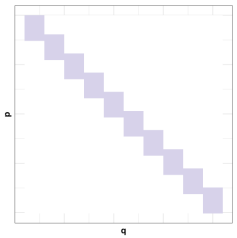
	$p = 1,000$				$p = 1,500$			
Model	$\hat{q}$	$\|\|\hat{\phi}\|\|_0$	$\|\|\mathbb{E}[X] - \hat{\mathbb{E}}[X]\|\|_F$	$\|\|\text{Cov}[x_i] - \widehat{\text{Cov}}[x_i]\|\|$	$\hat{q}$	$\|\|\hat{\phi}\|\|_0$	$\|\|\mathbb{E}[X] - \hat{\mathbb{E}}[X]\|\|_F$	$\|\|\text{Cov}[x_i] - \widehat{\text{Cov}}[x_i]\|\|$
	$q = 10$							
Flat	10.0	10000.0	73.5	125.3	10.0	10000.0	89.4	203.7
Normal-SS	10.0	1298.6	43.9	89.1	10.0	1931.4	54.2	180.7
MOM-SS	10.0	1296.6	43.5	80.7	10.0	1919.3	56.2	169.4
FastBFA	9.9	778.1	60.3	165.0	9.9	1157.8	72.8	247.7
LASSO-BIC	10.0	5288.7	54.9	270.2	10.0	8414.6	67.2	408.4
	$q = 100$							
Flat	100.0	100000.0	209.5	185.7	100.0	100000.0	259.2	280.2
Normal-SS	31.0	1228.6	109.0	144.6	56.4	1568.2	181.3	231.9
MOM-SS	9.7	856.8	79.4	143.3	9.2	745.4	105.0	245.6
FastBFA	83.6	1389.9	198.1	141.9	87.2	1763.9	208.2	211.3
LASSO-BIC	10.0	4787.3	54.1	271.4	10.0	7976.6	66.1	409.3

Simulation studies

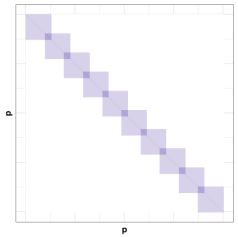
Harvard-MIT Center for Regulatory Science

Synthetic data **with** batch effects for $n = 200$, $q^* = 10$, $p = 250$ or 500 parameters, truly sparse loadings ϕ^*.

ϕ



$\phi\phi^\top + \mathcal{T}^{-1}$



	$p = 250$				$p = 500$			
Model	$\hat{q}$	$\|\|\hat{\phi}\|\|_0$	$\|\|\mathbb{E}[X] - \hat{\mathbb{E}}[X]\|\|_F$	$\|\|Z\phi^\top - \mathbb{E}[Z \mid \cdot]\hat{\phi}^\top\|\|_F$	$\hat{q}$	$\|\|\hat{\phi}\|\|_0$	$\|\|\mathbb{E}[X] - \hat{\mathbb{E}}[X]\|\|_F$	$\|\|Z\phi^\top - \mathbb{E}[Z \mid \cdot]\hat{\phi}^\top\|\|_F$
	$q = 10$							
Flat	10.0	2500.0	42.7	52.0	10.0	2500.0	54.8	68.2
Normal-SS	10.0	330.0	39.7	53.7	10.0	650.0	51.2	68.1
MOM-SS	10.0	330.0	39.2	61.3	10.0	650.0	49.6	86.1
ComBat-MLE	10.0	2500.0	127.2	143.3	10.0	2500.0	177.9	200.8
FastBFA	10.0	173.1	53.7	166.8	10.0	376.0	71.3	235.4
LASSO-BIC	10.0	1441.3	39.9	179.4	10.0	3159.1	50.0	254.2
	$q = 100$							
Flat	100.0	25000.0	96.8	100.6	100.0	25000.0	147.8	152.5
Normal-SS	10.0	765.8	45.7	54.8	10.6	1146.3	60.0	72.6
MOM-SS	10.0	740.4	63.8	72.4	10.0	1158.7	85.7	108.3
ComBat-MLE	100.0	25000.0	169.0	182.9	100.0	25000.0	232.7	252.4
FastBFA	10.0	337.0	51.9	168.3	11.3	681.8	75.8	247.9
LASSO-BIC	10.3	1374.0	39.6	178.9	10.3	2613.9	49.8	252.1

Simulation studies

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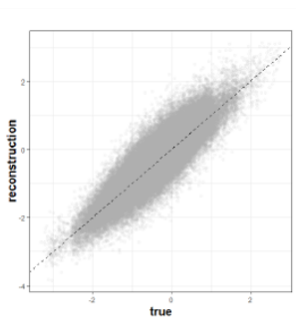
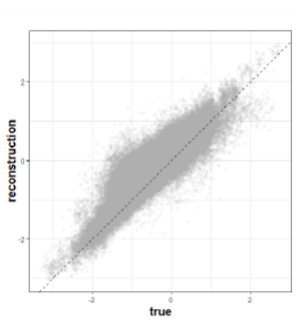
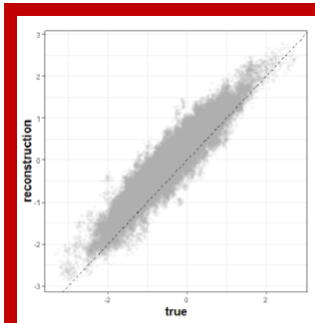


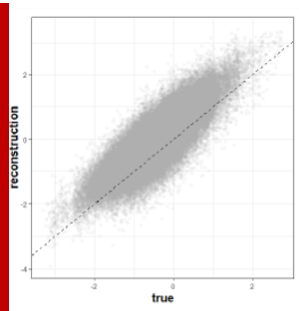
Flat Dense M



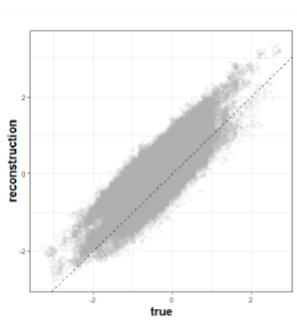
Normal-SS Dense M



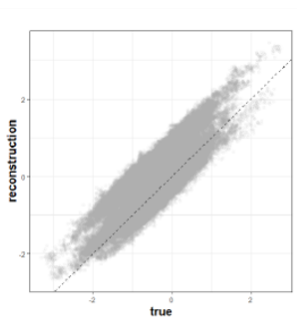
MOM-SS Dense M



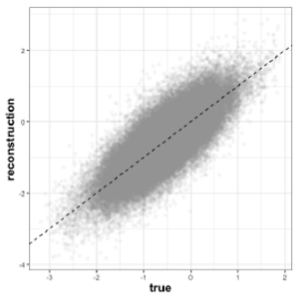
ComBat-MLE Dense M



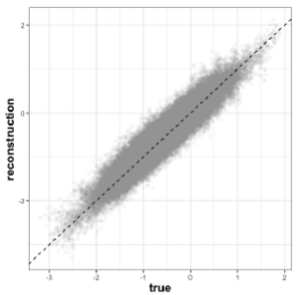
FastBFA Dense M



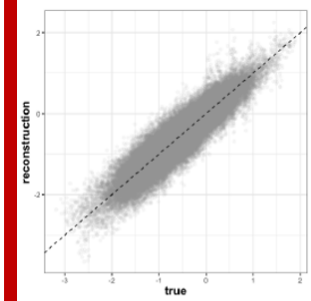
LASSO Dense M



Flat Sparse M



Normal-SS Sparse M



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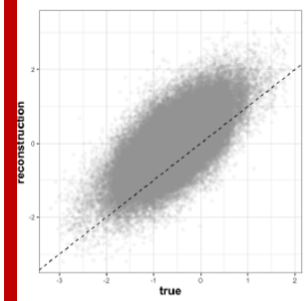

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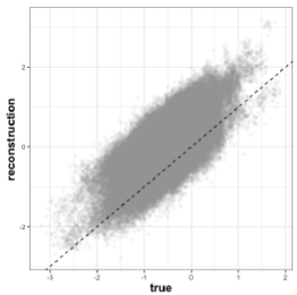

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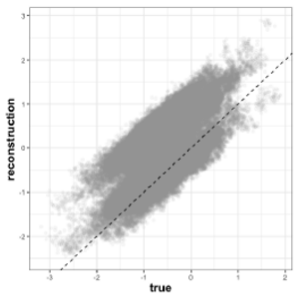

LASSO Sparse M

Simulation studies

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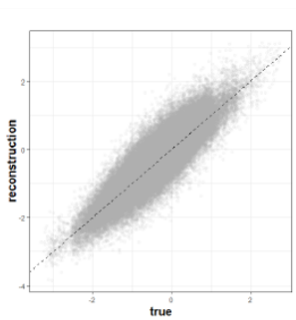
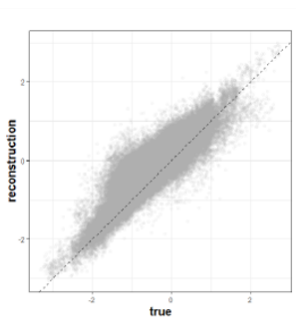
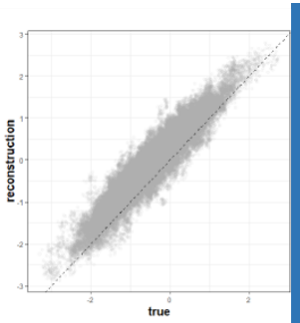


Flat Dense M



Normal-SS Dense M



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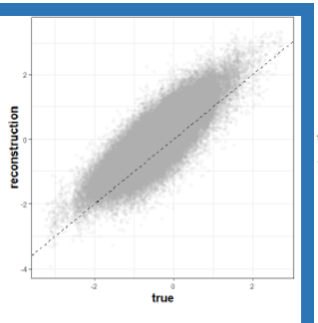
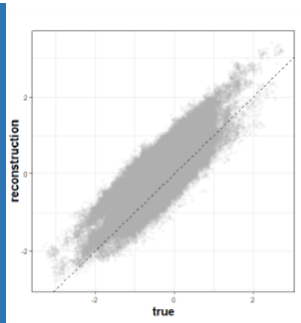


ComBat-MLE Dense M



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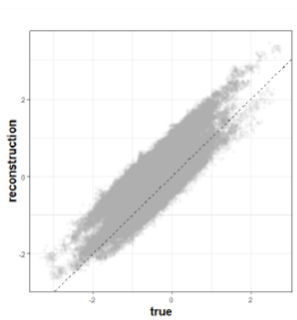
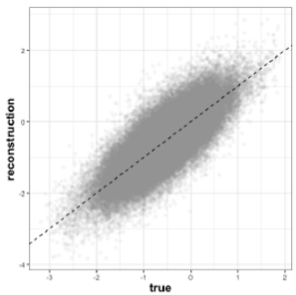
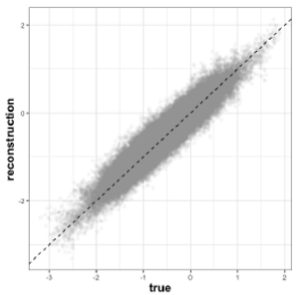


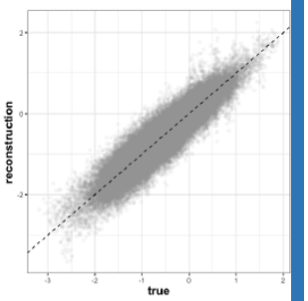
LASSO Dense M



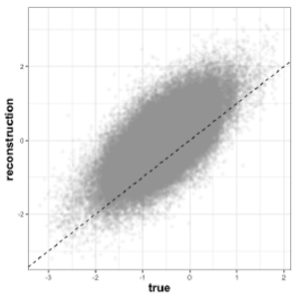
Flat Sparse M



Normal-SS Sparse M



MOM-SS Sparse M



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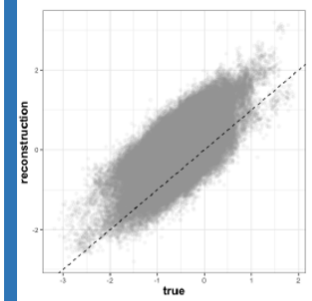
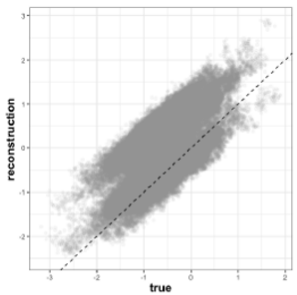


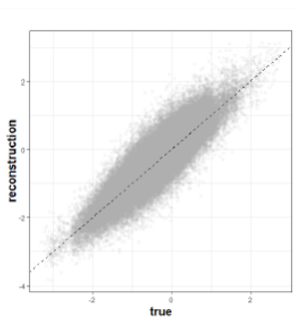
FastBFA Sparse M



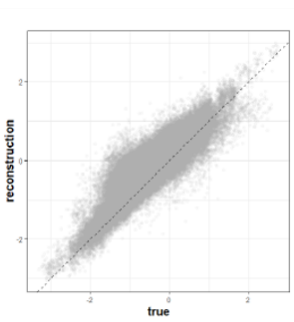
LASSO Sparse M

Simulation studies

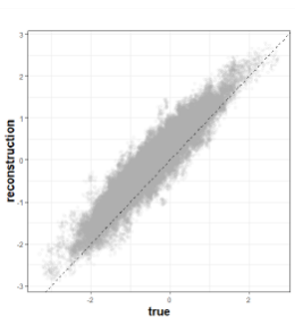
Harvard-MIT Center for Regulatory Science



Flat Dense M



Normal-SS Dense M



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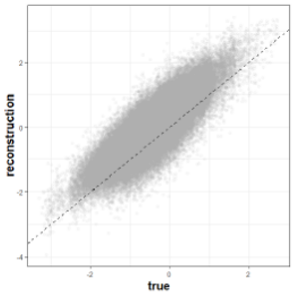
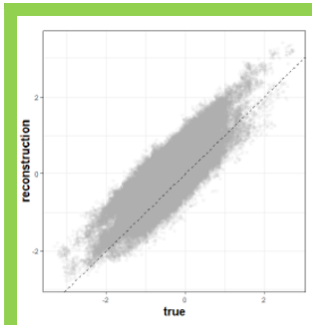
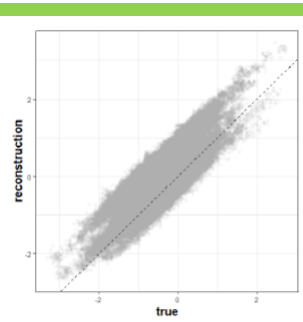


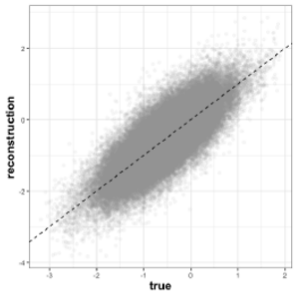
ComBat-MLE Dense M



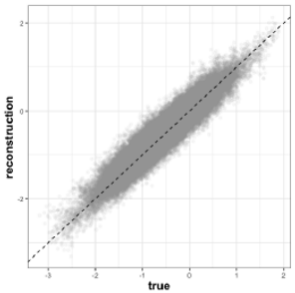
FastBFA Dense M



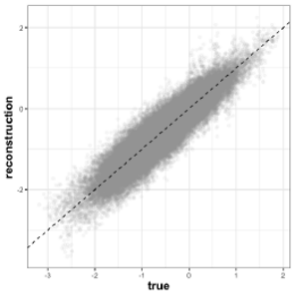
LASSO Dense M



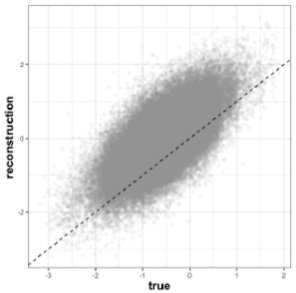
Flat Sparse M



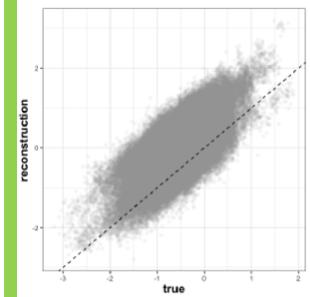
Normal-SS Sparse M



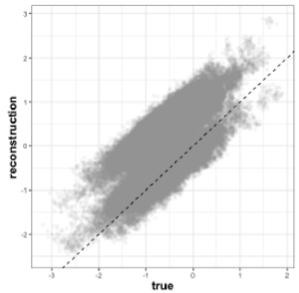
MOM-SS Sparse M



ComBat-SS Sparse M



FastBFA Sparse M

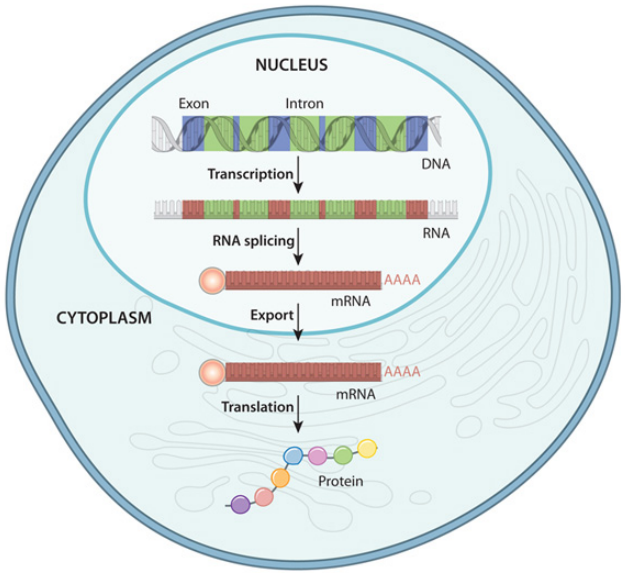


LASSO Sparse M

Gene expression

Gene expression

- It has been used as a drug discovery tool
- Key to understanding biological process such as cancer
- Useful for classifying cancer tumours into subtypes



Cancer datasets

Harvard-MIT Center for Regulatory Science

1. Ovarian cancer: `curatedOvarianData 1.16.0`, $p = 1,007$ genes
   1. Illumina Human microRNA array `E.MTAB.386`, $n_1 = 129$ patients.
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- Age at initial pathologic diagnosis has been used as covariate.

Ovarian Unsupervised

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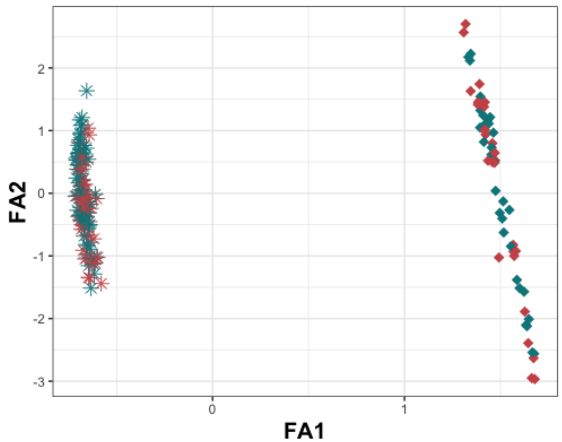
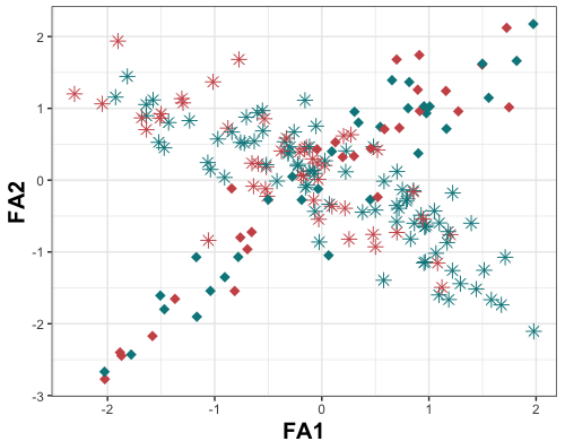
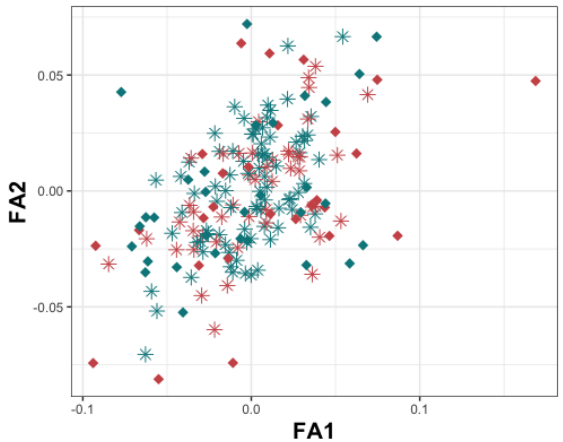
Ov, No correction



Ov, ComBat-MLE



Ov, MOM-SS



Lung Unsupervised

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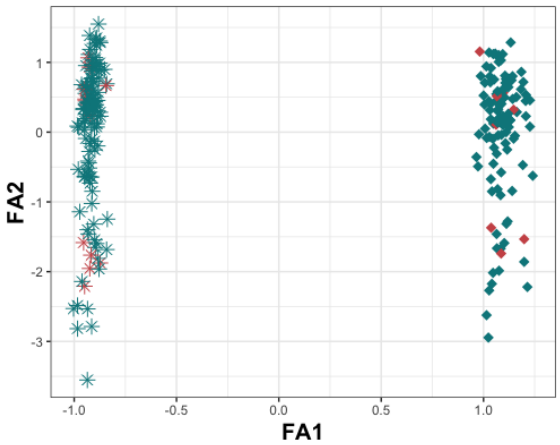
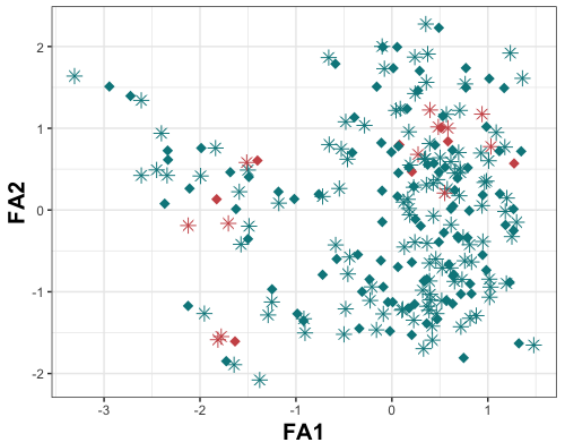
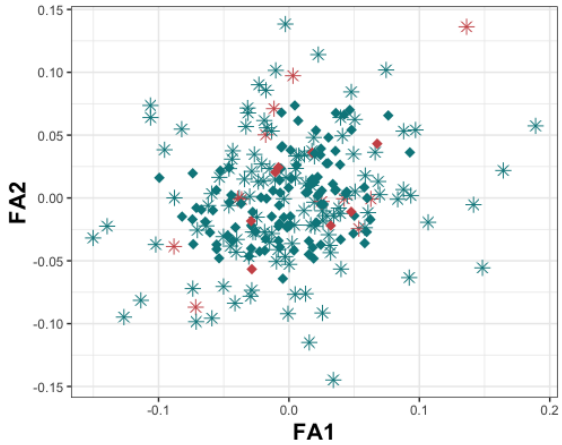
Lung, No correction



Lung ComBat-MLE



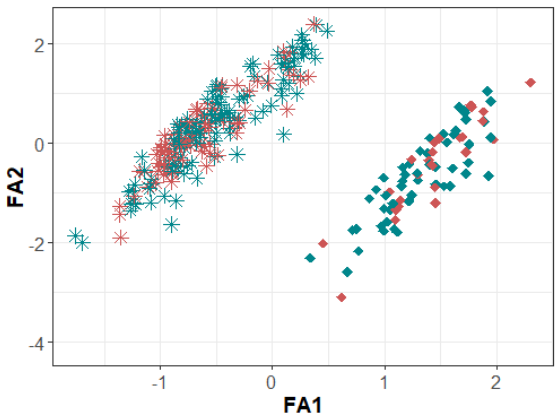
Lung MOM-SS



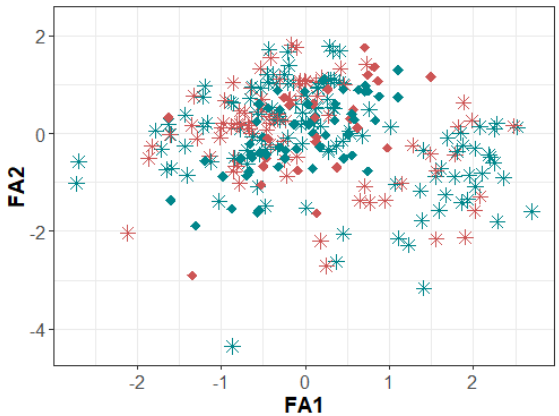
Colon Unsupervised

Harvard-MIT Center for Regulatory Science

Colon, No correction



Colon ComBat-MLE



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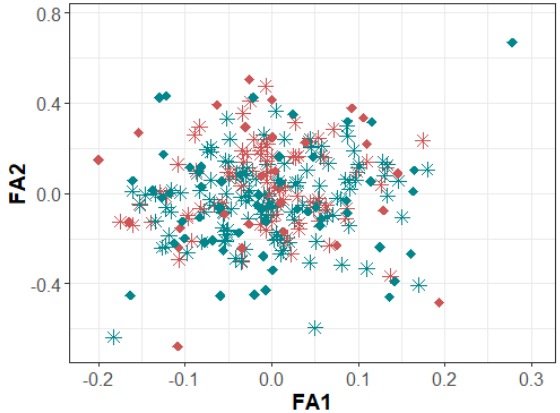

Supervised

Harvard-MIT Center for Regulatory Science

Expression data of cancer datasets. Supervised analysis for ovarian ($p = 1,007$ genes), lung ($p = 1,198$ genes) and colon ($p = 172$ genes) data sets.

	Ovarian			Lung			Colon		
	$\hat{q}$	$\lvert\hat{M}\rvert_0$	Concordance index	$\hat{q}$	$\lvert\hat{M}\rvert_0$	Concordance index	$\hat{q}$	$\lvert\hat{M}\rvert_0$	Concordance index
Batch 1-MLE 90%	67.1	67569.7	0.618	52.1	62415.8	0.461	52.9	9081.6	0.736
Batch 1-MLE 70%	27.0	27088.3	0.632	35.2	42169.6	0.471	17.0	2924.0	0.721
Batch 2-MLE 90%	40.4	40481.4	0.522	36.6	43607.2	0.522	48.1	8256.0	0.479
Batch 2-MLE 70%	23.4	23362.4	0.524	23.2	27913.4	0.419	23.3	4007.6	0.495
Flat	100.0	100700.0	0.634	100.0	119800.0	0.669	100.0	17200.0	0.594
Normal-SS	7.8	7854.6	0.568	11.0	13178.0	0.489	7.0	1204.0	0.621
MOM-SS	4.0	4028.0	0.588	74.0	88652.0	0.665	53.4	9184.8	0.764
ComBat-MLE 90%	101.0	101707.0	0.589	79.0	94642.0	0.688	67.0	11524.0	0.738
ComBat-MLE 70%	41.0	41287.0	0.588	30.0	35940.0	0.568	24.0	4128.0	0.734
ComBat-FastBFA	100.0	100700.0	0.527	100.0	119800.0	0.707	100.0	17200.0	0.582

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Harvard-MIT Center for Regulatory Science

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- R Packages
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