Multi-Way, Multi-View Learning

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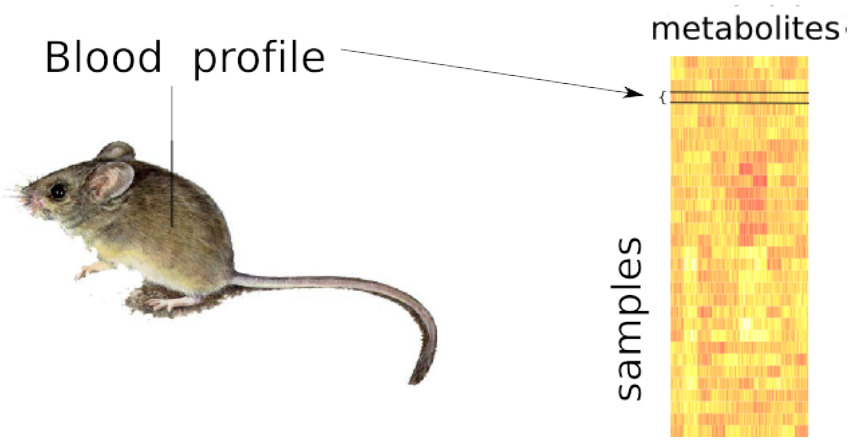
Metabolomics data

- Metabolomics: Diseases affect the concentrations of metabolites = chemical compounds
- Concentrations of > 100 metabolites (Mass Spectrometry)
- Covariates, find biomarkers for disease



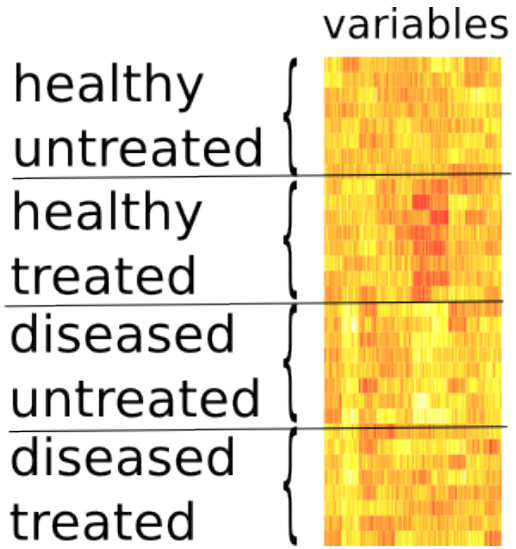
- Find features with differential concentration, confidence intervals

Multi-way experimental setups

- Current approach **One-way methods**: diseased-healthy comparison, only find biomarkers for disease
- **Additional covariates**: Medical treatment, gender, time-series, **multi-way**
  - ANOVA, linear model, MANOVA

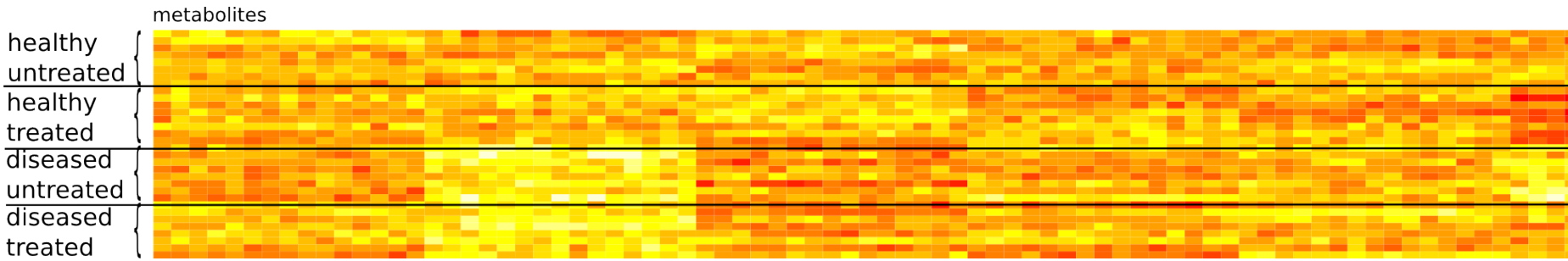
$$\mathbf{x} = \mu^x + \alpha_a^x + \beta_b^x + (\alpha\beta)_{ab}^x + \text{noise}.$$

  - μ^x grand mean
  - α_a^x, β_b^x main effects
  - $(\alpha\beta)_{ab}^x$ **Interaction effect** of covariates



Small sample-size problem

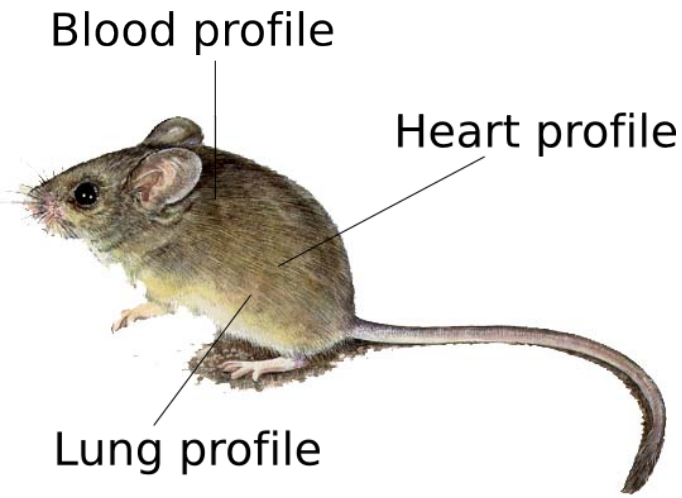
- High dimensionality
- Small number of samples (economical & ethical cost)
- Standard approaches do not work
- Uncertainty estimation crucial



- Strong dimensionality reduction
- Use prior knowledge: Metabolites form similarly behaving groups

Biological multi-source experiments

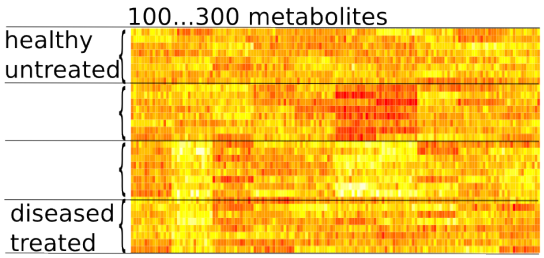
Metabolic profiles from several tissues



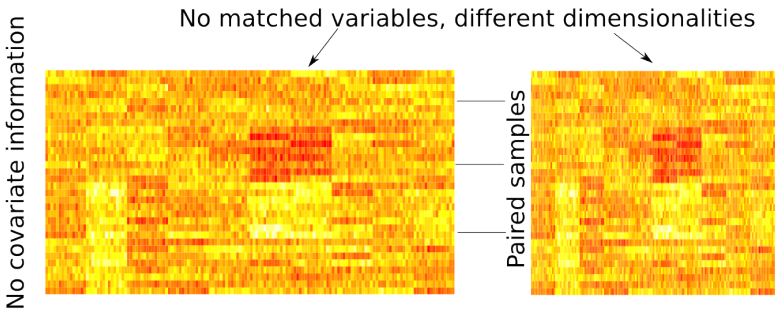
- Different metabolites in different tissues
- Same individual (pairing)
- Are there disease-related dependencies between the tissues?

Multi-Way, Multi-Source setups

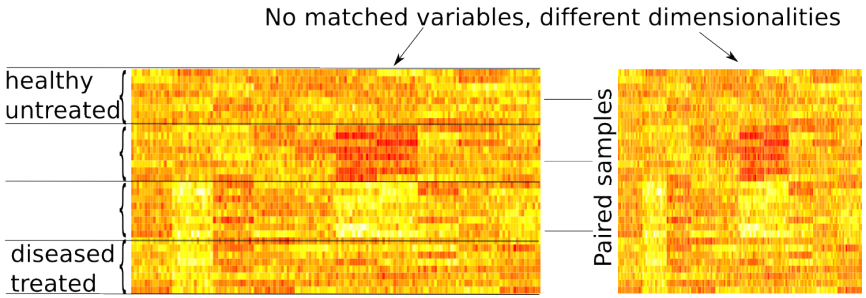
Multi-way analysis (ANOVA)



Multi-source analysis (CCA)



Multi-source, multi-way analysis



Multi-View Learning with multiple **independent** covariates

Decomposition into **shared** and **source-specific** covariate effects

IDEA: write a linear ANOVA-model where view is one covariate

$$\mathbf{x}_d = \boldsymbol{\mu}_d + \boldsymbol{\alpha}_a + \boldsymbol{\beta}_b + (\boldsymbol{\alpha\beta})_{ab} + \boldsymbol{\gamma}_d + (\boldsymbol{\alpha\gamma})_{ad} + (\boldsymbol{\beta\gamma})_{bd} + (\boldsymbol{\alpha\beta\gamma})_{abd} + \text{noise},$$

a and b are traditional covariates, disease and treatment

d denotes the view.

- Problem: sources $\mathbf{x}_d$ have different domains
- Possible when using dependencies between datasets (paired samples)
- f^x projects the effects to different domains by hierarchical latent varible modelling

$$\begin{aligned}\mathbf{x} &= \mu + f^x(\alpha_a + \beta_b + (\alpha\beta)_{ab}) + f^x(\alpha_a^x + \beta_b^x + (\alpha\beta)_{ab}^x) + \text{noise},\\ \mathbf{y} &= \mu + f^y(\alpha_a + \beta_b + (\alpha\beta)_{ab}) + f^y(\alpha_a^y + \beta_b^y + (\alpha\beta)_{ab}^y) + \text{noise}, \quad (1)\end{aligned}$$

IDEA: write a linear ANOVA-model where view is one covariate

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The Bayesian Multi-Way, Multi-View model

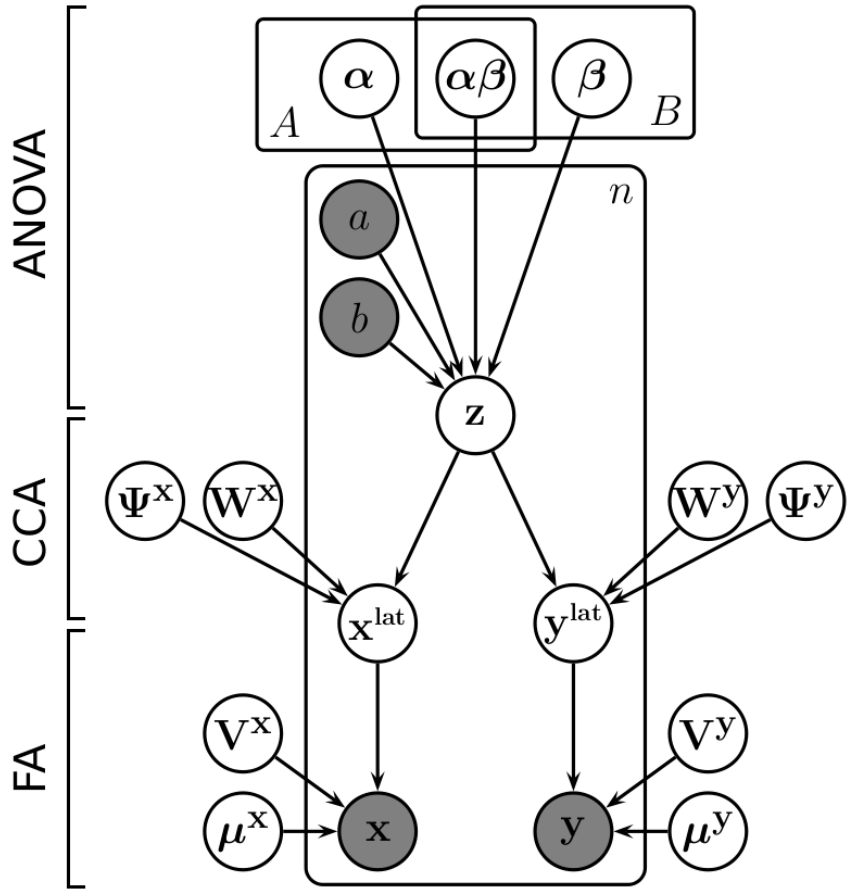
Linear model on shared components

Integrating the sources (bCCA)

Decomposition into shared and source-specific components

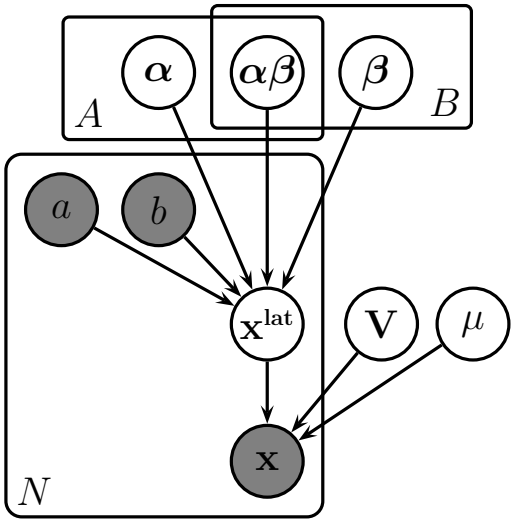
Dimension reduction by regularized clustering Factor analysis

Solved by Gibbs sampling



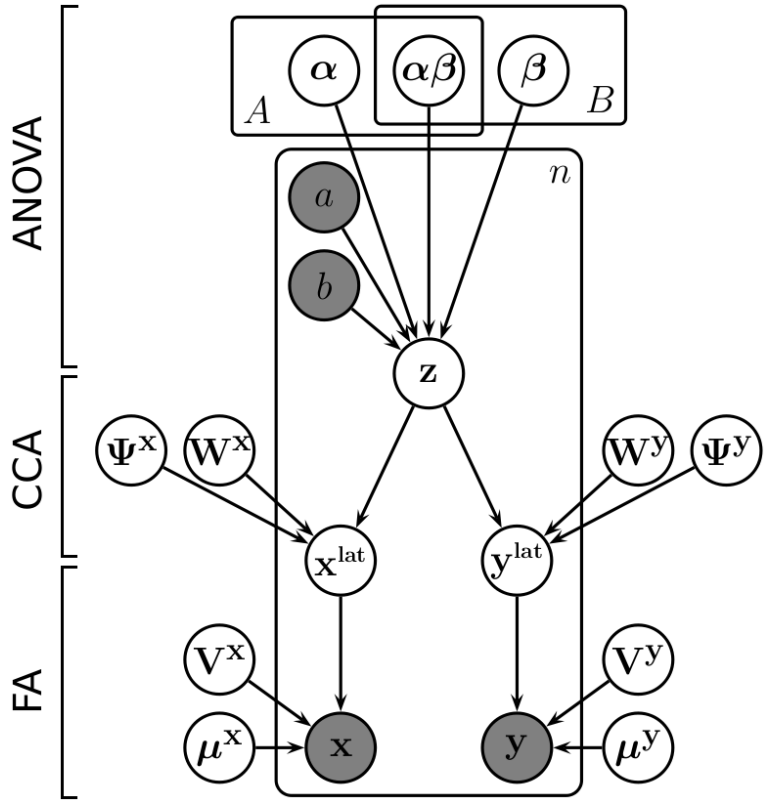
Single-source vs. Multi-source

Single source, multi-way model



[Huopaniemi et al., Two-way analysis of high-dimensional collinear data, ECML09 special issue of Data Mining and Knowledge Discovery: Volume 19, Issue 2 (2009), Page 261]

Multi-source, multi-way

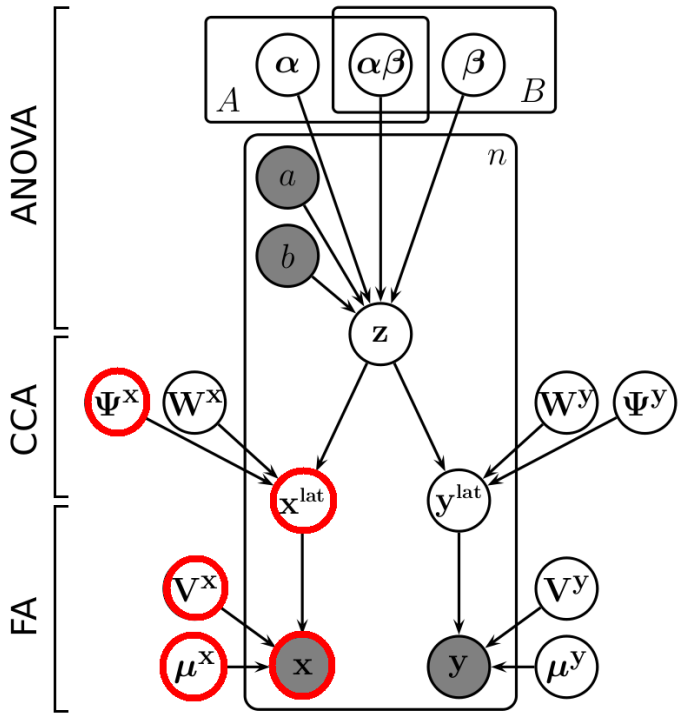


Regularized Factor Analysis

Factor analysis model

$$\mathbf{x}_j^{lat} \sim \mathcal{N}(0, \boldsymbol{\Psi}^x)$$
$$\mathbf{x}_j \sim \mathcal{N}(\boldsymbol{\mu}^x + \mathbf{V}^x \mathbf{x}_j^{lat}, \boldsymbol{\Lambda}^x) \,. \qquad (2)$$

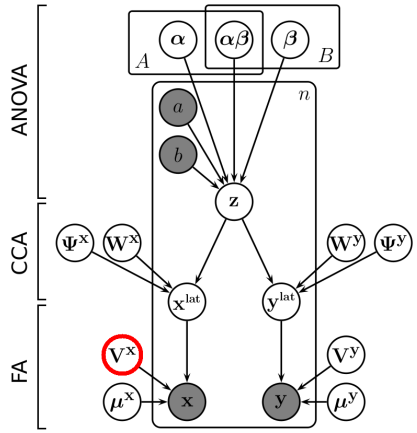
- $\boldsymbol{\Psi}^x$ comes from CCA
- Projection matrix $\mathbf{V}^x$ not invertible, regularize by forming it by clustering variables.
- Each variable comes from one factor(cluster) only
- Interpretation of ANOVA-effects for clusters of similarly behaving variables



Regularizing the projection matrix by clustering

- Each variable comes from exactly one factor
- Cluster variables to different factors by a mixture model
- Multiply by variable-specific scales λ_i

$$\mathbf{V}^x = \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & 0 & \lambda_2 \\ \vdots & \vdots & \vdots \\ 0 & \lambda_j & 0 \\ 0 & \lambda_{j+1} & 0 \\ \vdots & \vdots & \vdots \end{bmatrix}$$



Generative model of CCA for integrating the sources

Generative model of Bayesian CCA

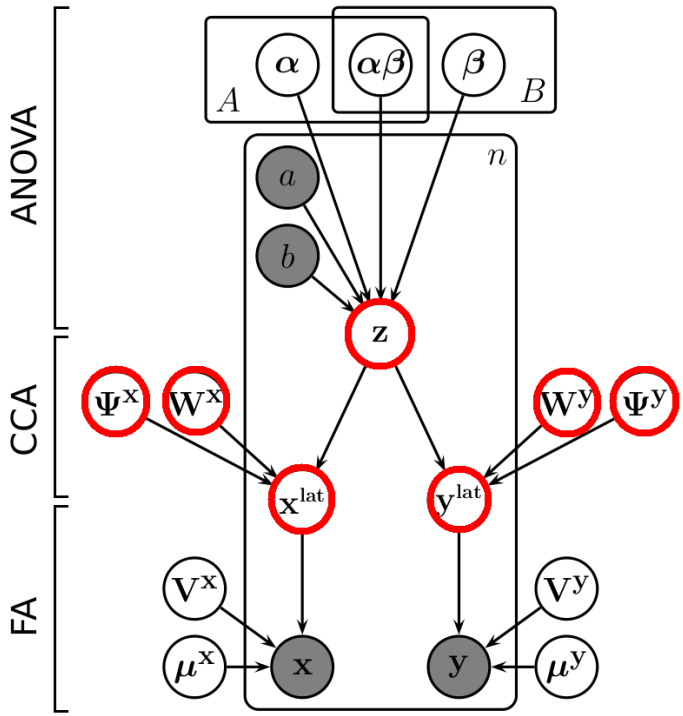
$$\mathbf{z}_j \sim N(0, \mathbf{I}),$$
$$\mathbf{x}_j^{lat} \sim N(\mathbf{W}^x \mathbf{z}_j, \boldsymbol{\Psi}^x), \qquad (3)$$

Projection matrix $\mathbf{W}^x$ has a hierarchical ARD (Automatic relevance determination)-prior

Now, the CCA generates a latent factor $\mathbf{x}_j^{lat}$

In normal bCCA $\mathbf{z}_j$ has a zero-mean prior

However, now the shared variable $\mathbf{z}_j$ will be given a linear model as prior



Bach and Jordan 2005, Klami and Kaski 2007

Covariate information as a linear model on the shared variable

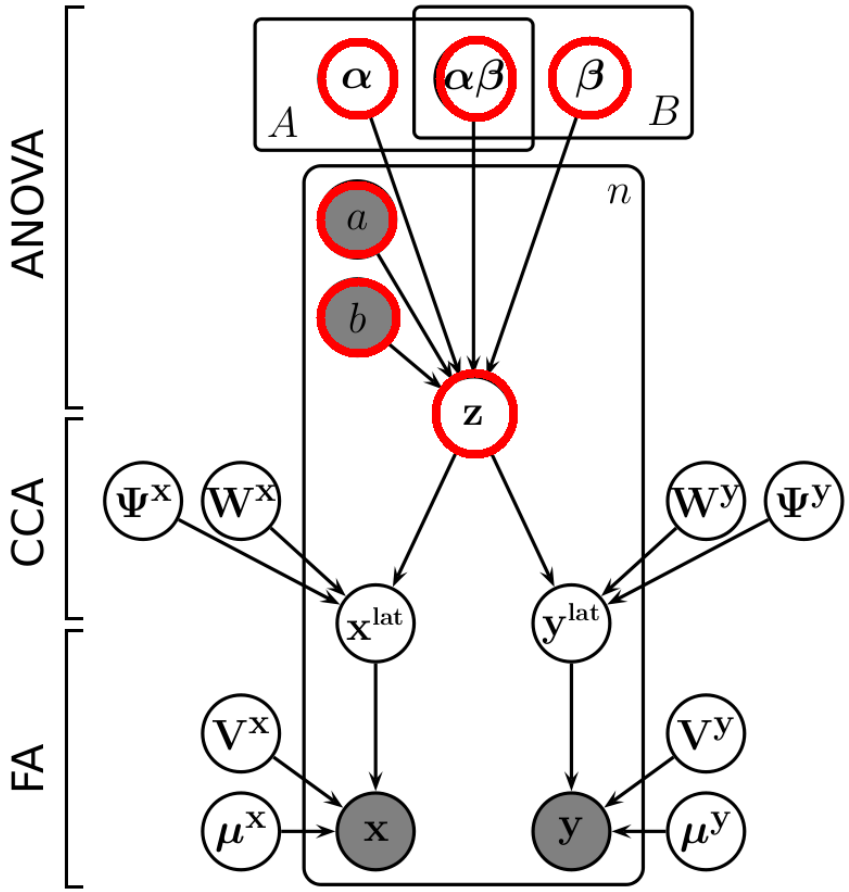
$$\mathbf{z}_j = \boldsymbol{\alpha}_a + \boldsymbol{\beta}_b + (\boldsymbol{\alpha}\boldsymbol{\beta})_{ab} + \boldsymbol{\epsilon}_j, \quad (4)$$

a and b are the observed covariates

Note that the baseline (grand mean) $\boldsymbol{\mu}_x$ is on the lower level

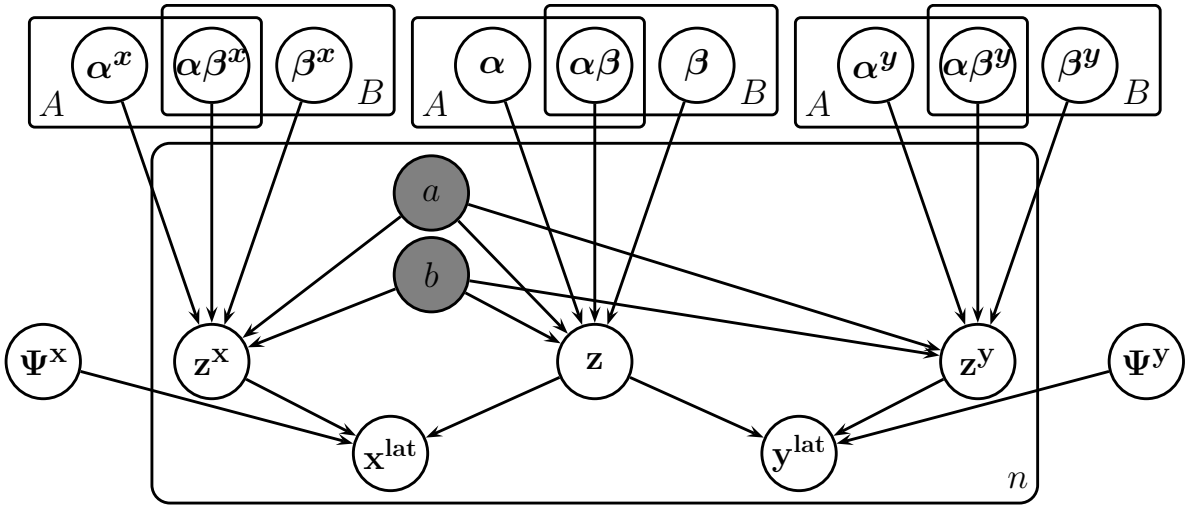
Centering $\boldsymbol{\mu}_x$ to the control group (healthy, untreated)

$\boldsymbol{\alpha}_a$ models the effect of disease
$\boldsymbol{\beta}_b$ treatment
$(\boldsymbol{\alpha}\boldsymbol{\beta})_{ab}$ interaction



Decomposition into shared and source-specific parts

Estimate the shared effect, and the source-specific effects



$$\mathbf{z}_j = \boldsymbol{\alpha}_a + \boldsymbol{\beta}_b + (\boldsymbol{\alpha\beta})_{ab} + \boldsymbol{\epsilon}_j, \tag{5}$$

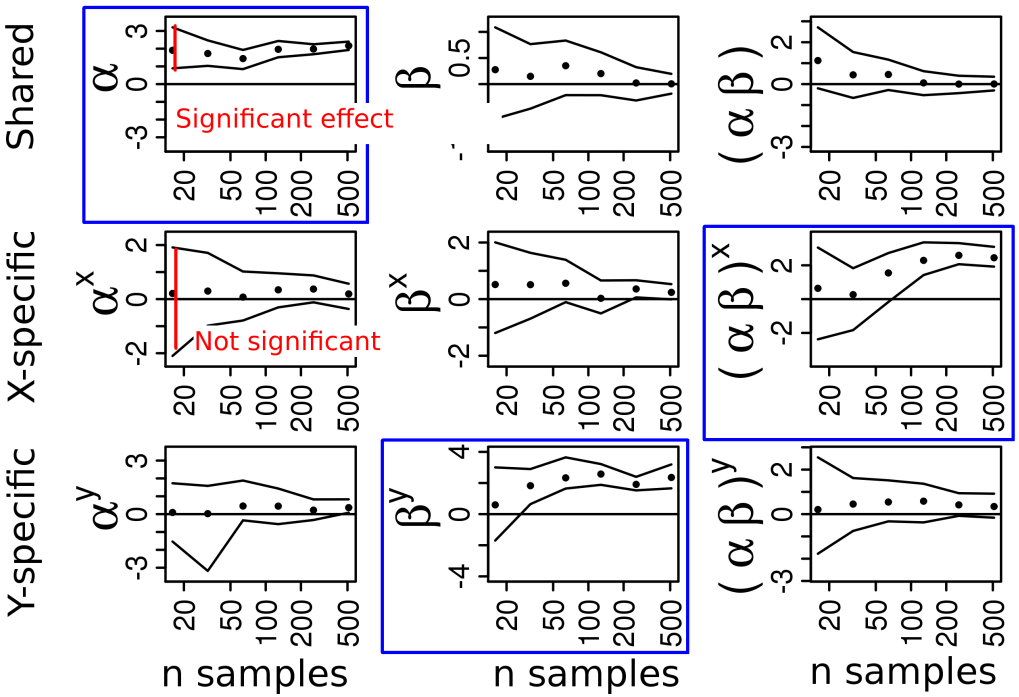
$$\mathbf{z}^x_j = \boldsymbol{\alpha}^x_a + \boldsymbol{\beta}^x_b + (\boldsymbol{\alpha\beta})^x_{ab} + \boldsymbol{\epsilon}^x_j, \tag{6}$$

$$\mathbf{x}^{lat}_j \sim \mathcal{N}(\mathbf{W}^x_{\text{shared}}\mathbf{z}_j + \mathbf{W}^x_{\text{specific}}\mathbf{z}^x_j, \Psi^x). \tag{7}$$

In practice, solve one shared and two specific components by fixing columns of $\mathbf{W}^x$ to zero.

How many samples needed to find effects from data generated by the model?

Generated 200-dim datasets with a multi-way, multi-source setup

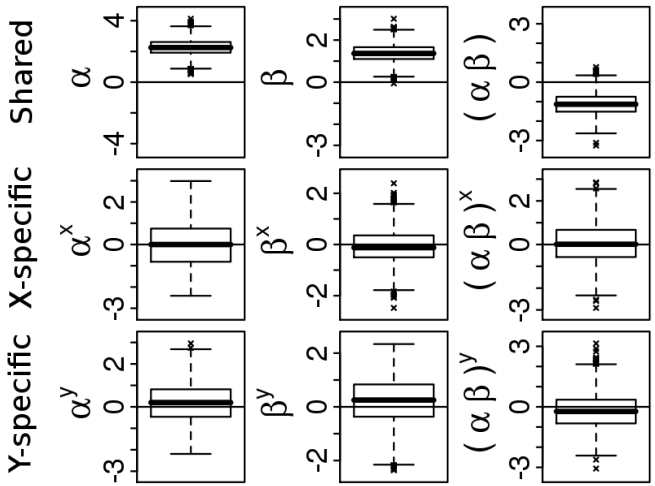


The method finds the generated effects even with small sample size

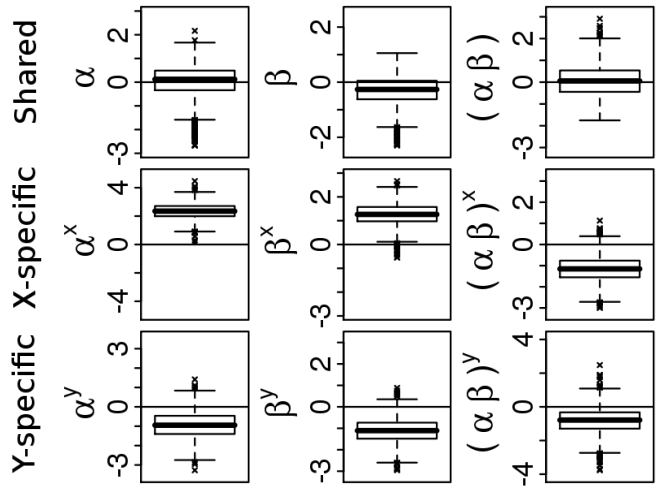
Lung cancer study: Lipidomic profiles, blood, lung, heart

Diseased - healthy, treated - untreated.

α disease effect, β treatment effect, $\alpha\beta$ interaction effect



Experiment 1



Experiment 2

Blood - lung (disease tissue)

Shared disease and treatment effects found

Blood - heart (no disease expected)

Only source-specific effects found

Conclusions

- Biological experiments often have a multi-way, multi-source experimental setup
- Our method finds shared and source-specific covariate effects for similarly behaving groups of variables
- Can deal with the main restriction: $n \ll p$
- Shared effects in different domains can be found in shared-space

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