Training course 3: Bayesian variable selection approach for structured variables.

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Outline

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Introduction

Objectives are:

- to present a Bayesian variable selection approach developed for structured variables,
- to present results on simulated datasets,
- to apply on a subset of your data.

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Context

Dependence among covariates may be induced by various factors in different applications:

- Disease mapping: structure in space and time for covariates measured over time at adjacent locations,
- Genetic: spatial dependence among molecular markers positioned at adjacent positions along genome,
- Genomic: dependence among genes belonging to same pathways,
- Functional MRI: spatial dependence among measures in connected regions in the brain,
- ...

↬ Most of these dependence structures may be depicted by an **undirected graph**.

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Statistical point of view

Such information may:

- help in the model building process,
- increase the statistical power to detect true associations,
- improve the predictive power.

Objective

To develop statistical methods incorporating the graph structure to simultaneously select the relevant variables and estimate their associated effects.

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Existing methods

In frequentist context:

- Approaches based on penalized likelihood methods (Li and Li, 2008, 2010):

↬ smoothness at the regression coefficient level by integrating a graph information.

In Bayesian context:

- Spike-and-slab prior on the regression coefficients with an Ising prior (prior considering graph information) on the variable selection indicators (Li and Zhang, 2010; Vannucci and Stingo, 2010),
- Priors on shrinkage parameters for global-local priors (Kowal et al., 2019)

↬ Smoothness at the variable selection indicator or at the shrinkage parameter levels,

- Bayesian version of the frequentist approaches (Zhou and Zheng, 2013).

The proposed approach:

We propose combining a Gaussian Markov random field (GMRF) prior with a global-local shrinkage prior to select graph-structured variables in the same spirit as Faulkner and Minin (2018).

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Statistical model

Linear regression model

$$y = X\beta + \varepsilon$$

where

- $y = (y_1, \ldots, y_n)'$ a n-dimensional vector of observations,
- $\beta = (\beta_1, \ldots, \beta_p)'$ a p-dimensional vector of regression coefficients,
- X a $n \times p$ matrix of predictor variables,
- $\varepsilon = (\varepsilon_1, \ldots, \varepsilon_n)'$ a n-vector of residuals assumed to follow a multivariate Gaussian distribution $\mathcal{N}_n(0, \sigma^2 I_n)$.

Graph information for the p predictors:

$\Rightarrow$ $\mathcal{G}$ an **undirected graph** such that $\mathcal{G} = \bigcup_{i=1}^{I} \mathcal{G}_i = \bigcup_{i=1}^{I} (V_i, E_i)$ is a disjoint union of I graphs where V_i is a finite set of vertices (or predictors) associated to the graph i, and E_i is the associated set of edges.

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Statistical model

Bayesian hierarchical model

$$
\begin{aligned}
y|\beta,\sigma^2 &\sim \mathcal{N}_n(X\beta,\sigma^2 I_n)\\
\beta_j-\beta_{j'}|\tau^2_{jj'},\,\lambda^2 &\sim \mathcal{N}(0,\lambda^2\tau^2_{jj'}) \text{ for } (j,j')\in\bigcup_{i=1}^{I} E_i\\
\beta_j|\tau^2_j,\,\lambda^2 &\sim \mathcal{N}(0,\lambda^2\tau^2_j) \text{ for } j\in\mathcal{S}\\
\tau_{jj'} &\sim \mathcal{C}^+(0,1) \text{ for } (j,j')\in\bigcup_{i=1}^{I} E_i\\
\tau_j &\sim \mathcal{C}^+(0,1) \text{ for } j\in\mathcal{S}\\
\lambda &\sim \mathcal{C}^+(0,\sigma)\\
\sigma^2 &\sim \mathcal{IG}(s,r)
\end{aligned}
$$

With $\mathcal{S}$ is the set of indices associated to one representative of each graph, $\mathcal{C}^+$ the half-Cauchy distribution, $\mathcal{IG}$ the inverse-gamma distribution.

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Statistical models

HS-GMRF

$$\beta_j - \beta_{j'} | \tau^2_{jj'}, \lambda^2 \sim \mathcal{N}(0, \lambda^2 \tau^2_{jj'}) \text{ for } (j, j') \in \bigcup_{i=1}^{I} E_i$$

- $\tau^2_{jj'}$: local shrinkage parameters providing flexibility in the amount of shrinkage and smoothness of the coefficients of the connected variables,
- λ^2: global parameter performing shrinkage on all coefficients.

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Statistical models

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- $\tau^2_{jj'}$: local shrinkage parameters providing flexibility in the amount of shrinkage and smoothness of the coefficients of the connected variables,
- λ^2: global parameter performing shrinkage on all coefficients.

HS-GMRF-sign

$$\beta_j - \delta_{jj'} \beta_{j'} | \tau^2_{jj'}, \lambda^2 \sim \mathcal{N}(0, \lambda^2 \tau^2_{jj'}) \text{ for } (j, j') \in \bigcup_{i=1}^{I} E_i$$

- $\delta_{jj'}$: the correlation sign among X_j and X'_j.

Both models are inferred with a Markov chain Monte Carlo algorithm.

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Simulated datasets

Objective

To evaluate the performance of the proposed approaches for varying number of connected predictors (q), varying level of correlation among them (ρ), varying values of regression coefficients (3 simulation models), and two designs (1 and 2).

Design	ρ	q	**Design**	ρ	q
1	0.5	low (126 edges)	2	0.5	low (63 edges)
1	0.5	high (238 edges)	2	0.5	high (119 edges)
1	0.9	low (126 edges)	2	0.9	low (63 edges)
1	0.9	high (238 edges)	2	0.9	high (119 edges)

Design 1: all covariates are connected / **Design 2**: half of the covariates are connected and the remaining are not.

A total of 24 scenarios were analyzed by four methods: horseshoe (HS) , HS-GMRF, HS-GMRF-sign, spike-and-slab with Ising prior for $n = 100$ observations and $p = 140$ covariates. HS model refers to the model assuming a HS prior (Carvalho et al., 2010) on the regression coefficients (no structure information).

Simulated datasets

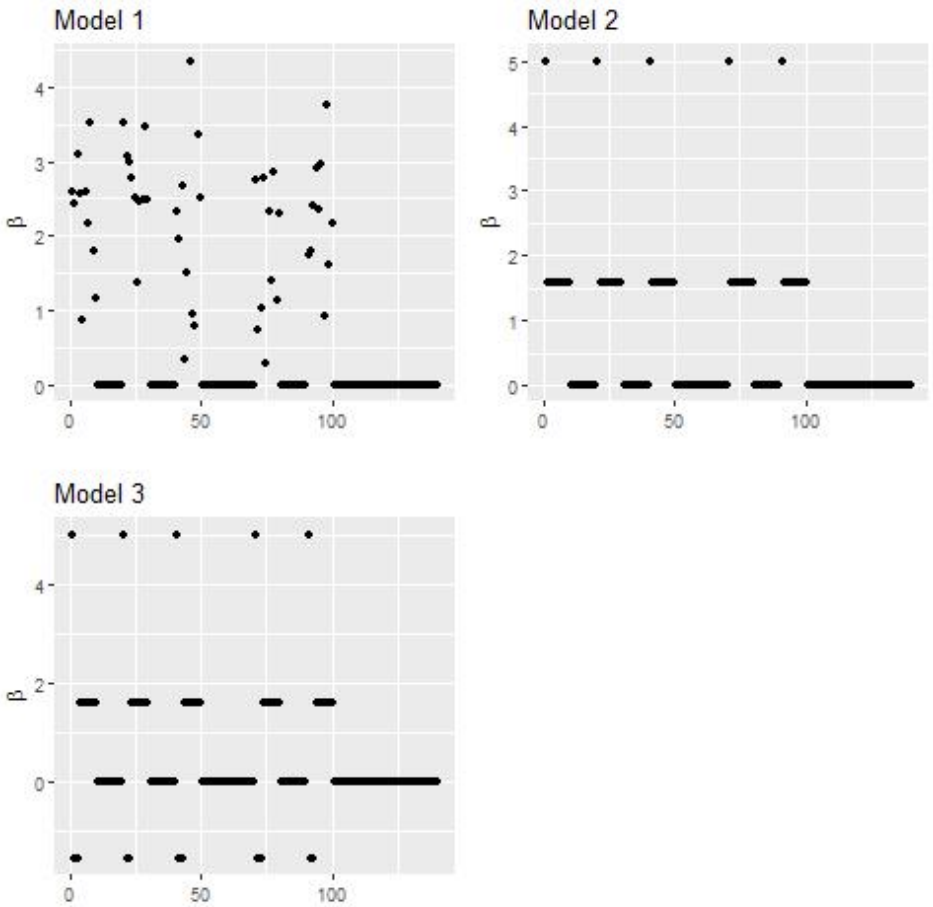

Figure 1: Simulated βs for the 140 covariates under simulation models 1, 2, and 3.

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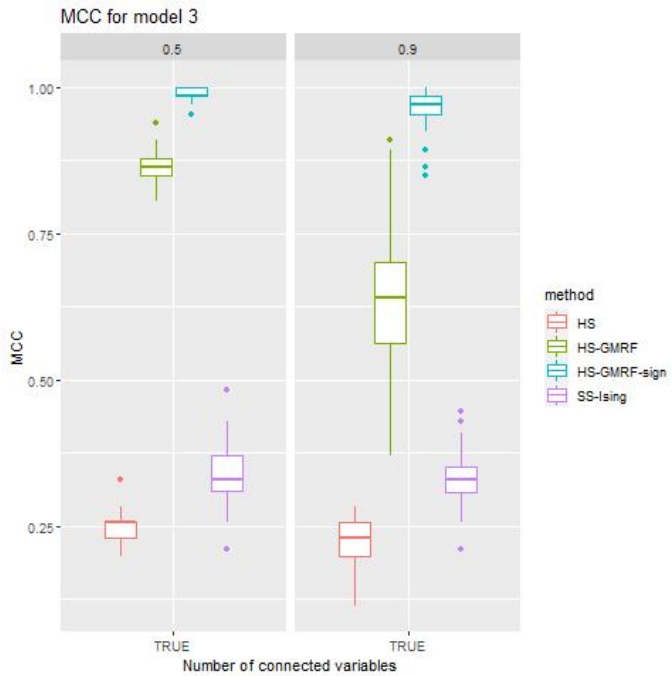
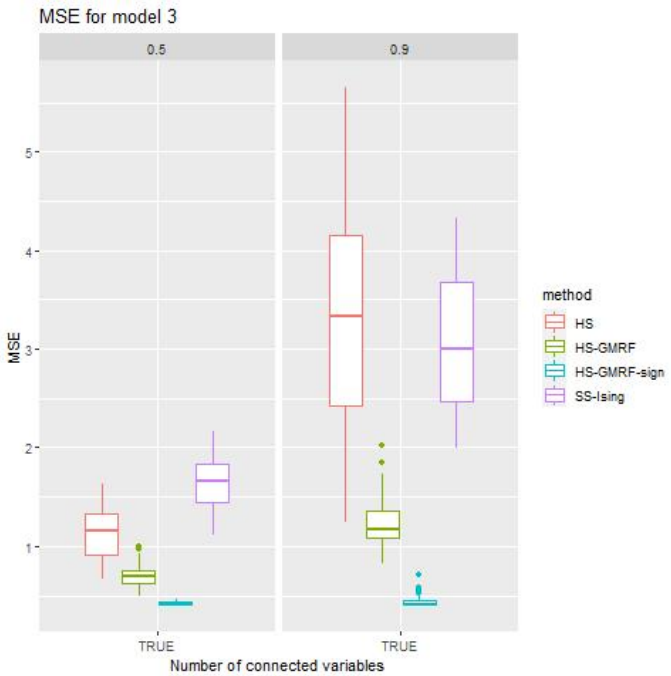
Results

Boxplots of Matthews correlation coefficients (MCC) (a combined measure of the overall variables selection accuracy) on the left and mean squared errors (MSE) for model simulation 3 under design 1:





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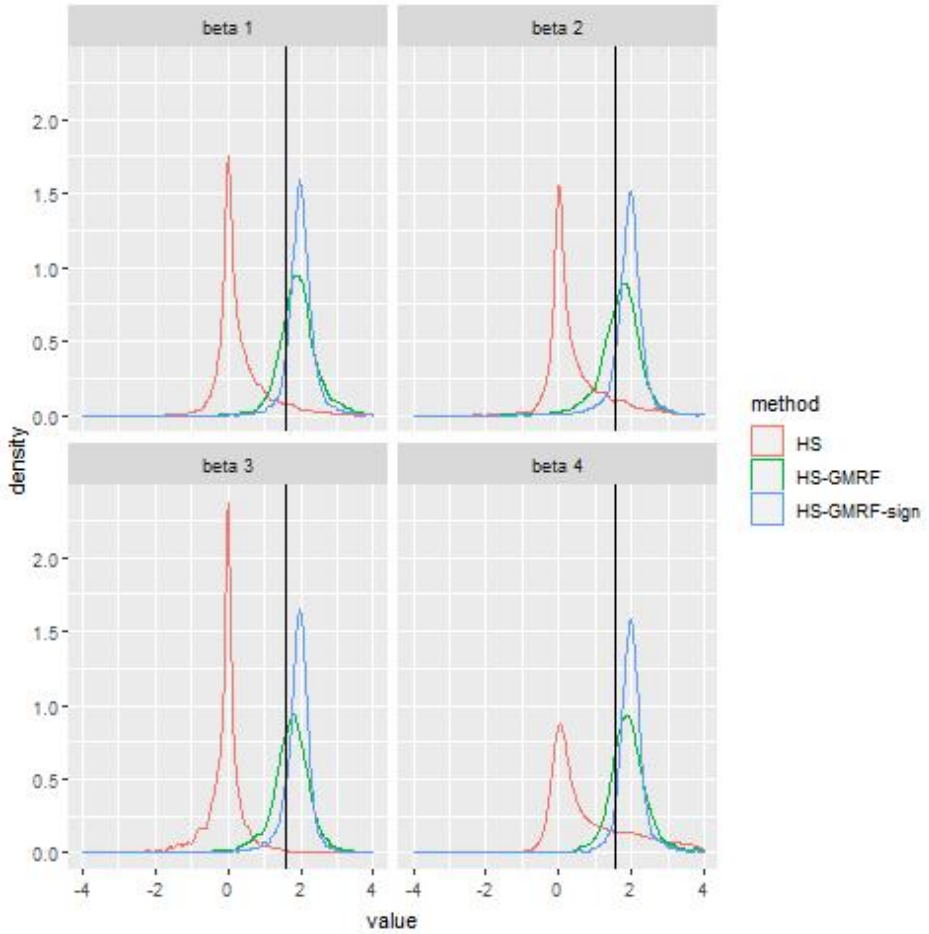
Results

Posterior densities for four βs for HS, HS-GMRF, and HS-GMRF-sign models:



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Results

By taking into account the structure information among the covariates the proposed method gives better results in terms of selection and estimation for all scenarios compared to the other approaches.

- **Higher number of edges**: helps the selection and estimation however when the correlation is high it encourages similar estimated values for the coefficients associated to highly correlated predictors

$\Rightarrow$ Hypothesis that highly correlated predictors have similar effects.

- **Integrating the correlation** sign among the predictors improves the results.
- The selection and estimation of regression coefficients for the non connected variables is the same as the HS prior $\Rightarrow$ **flexibility** in the shrinkage due to both local and global parameters.
- In terms of interpretation this approach allows identifying groups of correlated variables $\Rightarrow$ results **more interpretable**.

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Two real datasets

Two datasets were analyzed:

- Application 1: The study of riboflavin production based on gene expressions.
- Application 2: The study of fat content based on near-infrared absorbency spectra of meat samples.

- Graph obtained from partial correlations.
- Graph obtained from *a priori* knowledge.

- Identification of groups of correlated genes, better predictions (results obtained with a cross-validation procedure).
- Identification of wavelengths, better predictions (results obtained with a cross-validation procedure).

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Context

Multi-Omic inTegrative Analysis (MOTA) approach was developed to analyze multi-omic data for ranking candidate disease biomarkers (Fan et al., 2020).

Data

- Three sets of omic data generated from the same set of samples: metabolomics (M), glycomics (G), and proteomics (P).
- Three study cohorts (TU, GU1, GU2).

Principle

- Network obtained from intra-omic and inter-omic connections

↬ MOTA score combines z-scores obtained from p-values calculated using Student's t-tests.

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Ranking of HCC-associated metabolites

Table 3. Biomarker candidates overlapping between the GU1, TU, and combined TU and GU1 datasets ranked by *t*-test, iDINGO, and MOTA.

Rank	GU1 Cohort	TU Cohort	GU1+TU Cohort	No. of Overlaps
		Ranking using **Student *t*-Test (*p*-Value)**		
1	ethanolamine	glutamic acid	ethanolamine	
2	phenylalanine	lactic acid	sorbose	
3	sorbose	alpha tocopherol	citric Acid	
4	pyroglutamic acid	valine	isoleucine	
5	glycine	ethanolamine	threitol	2
6	linoleic acid	alpha-D-glucosamine 1-phosphate	ribose	
7	creatinine	norvaline	malic acid	
8	lauric acid	citric Acid	phenylalanine	
9	ribitol /arabitol	norleucine	stearic acid	
10	threitol	sorbose	trans-aconitic acid	
		Ranking using **iDINGO**		
1	linoleic acid	norvaline	valine	
2	isoleucine	cystine	ethanolamine	
3	leucine	sorbose	butanediol	
4	proline	tagatose	ribose	
5	ethanolamine	isoleucine	glycine	
6	valine	trans-3-hydroxy-L-proline	sorbose	2
7	glutamic acid	N,N-dimethyl-1-4-phenylenediamine	tyrosine	
8	sorbose	cholesterol	malic acid	
9	aspartic acid	butanediol	isoleucine	
10	glycine	arachidic acid	tagatose	
		Ranking using **MOTA**		
1	tyrosine	alpha tocopherol	alpha tocopherol	
2	alpha tocopherol	tyrosine	ethanolamine	
3	pyroglutamic acid	ethanolamine	glycine	
4	glycine	creatinine	lactic acid	
5	ethanolamine	tyramine	creatinine	
6	phenylalanine	mimosine	tyrosine	4
7	citric acid	lactic acid	cholesterol	
8	threitol	cholesterol	tyramine	
9	tyramine	threitol	citric Acid	
10	aspartic acid	ribose	isoleucine	

Note: Metabolite candidates that appeared in the top-10 ranked lists of all three cohorts are highlighted with the same color.

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Results for metabolomics data

Results from MOTA select metabolites which were not identified by the other approaches:

- MOTA considers information from all the three platforms as well as the relationships among them

↬ Example of **tyrosine** which is identified by MOTA but has a high p-value with Student t-test $\Rightarrow$ **tyrosine** highly connected with low-p-value proteins and glycans

The proposed approach may be an alternative approach to select significant markers while considering relationships among the three sets of omic data through an undirected graph.

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Data

Focus on TU cohort with a total of 66 metabolites, 82 glycans, and 100 proteins for 86 patients. For the following we will note X the scaled 86×248 matrix of predictors such that:

$$X = [M, G, P]$$

and Y the 86 vector of binary observations with 0 for CIRR and 1 for HCC.

Objective is to identify predictors related to the disease status:

- ↬ Multivariable approaches to analyze simultaneously all markers using penalized approaches such as Lasso or horseshoe (HS) prior

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Univariate analysis

As a first step we also perform univariate analyses for X the scaled matrix of the three sets of omic data:

```
> res.student <- apply(X, 2, function(c) t.test(c~Y)$p.value)
> fdr.student <- p.adjust(res.student, method =  "fdr")
> head(sort(fdr.student))
```

```
[33032] L-glutamic acid 2                    P00747                    P02743
           0.0001570735              0.0221825895              0.0221825895
                 P13598                    P19320                    P29622
           0.0221825895              0.0221825895              0.0221825895
```

```
> head(sort(fdr.student[1:ncol(X.tu)]))  # focus on metabolites
```

```
                     [33032] L-glutamic acid 2
                                  0.0001570735
            [107689] L-(+) lactic acid [6.851]
                                  0.0317582528
                    [2116] alpha tocophereol
                                  0.0903087788
                  [700] ethanolamine [9.879]
                                  0.0993613578
[740] alpha-D-glucosamine 1-phosphate¬† [16.61]
                                  0.1021115952
                                    L-Valine 2
                                  0.1116471870
```

Mutivariable analysis

Lasso regression with the package glmnet

```
> library(glmnet)
> lambdas <- 10^seq(2, -3, by = -.1)
> # cross-validation procedure
> cv_lasso <- cv.glmnet(X, Y, alpha = 1, lambda = lambdas,
+                       family = "binomial")
> # largest value of lambda such that error is
> # within 1 standard error of the minimum
> optimal_lambda <- cv_lasso$lambda.1se
> lasso_model <- glmnet(X, Y, alpha = 1, lambda = optimal_lambda,
+                       family = "binomial")
> which(lasso_model$beta[,1] != 0)
[33032] L-glutamic acid 2
                       1
```

- Only one metabolite is selected

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Mutivariable analysis

HS regression with the package bayesreg

```
> library(bayesreg)
> HS.model <- bayesreg(Y~X, data = data.frame(Y, X),
+                      prior = "hs",n.samples = 10000,
+                      burnin = 5000, model = "binomial")
> library(coda)
> # posterior means
> beta.hs <- rowMeans(HS.model$beta[,-(1:5000)])
> # Highest posterior density (HPD) intervals
> ci <- t(apply(HS.model$beta[,-(1:5000)], 1, function(r) HPDinterval(as.mcmc(r), prob =0.95)))
> colnames(X)[which(apply(sign(ci), 1, prod) == 1)]
character(0)
```

- No metabolite is selected

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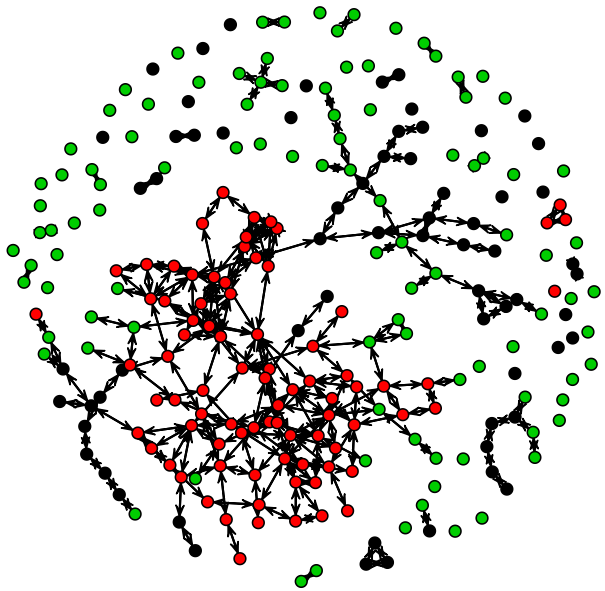
Undirected graph

In the objective to infer an undirected graph, the partial correlations were computed. A threshold of 0.45 was applied to obtain the following network:

Network

```
> library(network)
> plot(network(G), vertex.col = col.data)
```

black = Metabolomics, red = Glycomics, green = Proteomics



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HS-GMRF-sign model

HS-GMRF-sign model was applied:

```
> MRF_prob <- MRF_prob(Z = as.numeric(Y)-1, X = X, C = C,iter = iter)
> burn <- 5000
> iter <- 10000
> # posterior means
> beta.MRF <- colMeans(MRF_prob$theta_store[-(1:burn),][seq(1,iter-burn, by = 10),])
> # Highest posterior density (HPD) intervals
> ci.prob.95 <- t(apply(MRF_prob$theta_store[-(1:burn),][seq(1,iter-burn, by = 10),],
+                   2, function(r) HPDinterval(as.mcmc(r), prob = 0.95)))
> head(colnames(X)[which(apply(sign(ci.prob.95), 1, prod) == 1)])
[1] "[33032] L-glutamic acid 2"          "[107689] L-(+) lactic acid [6.851]"
[3] "[2116] alpha tocophereol"           "Tagatose 1"
[5] "[1101] L- sorbose 2 [17.235]"       "[304] cholesterol [27.555]"
> ci.prob.90 <- t(apply(MRF_prob$theta_store[-(1:burn),][seq(1,iter-burn, by = 10),],
+                   2, function(r) HPDinterval(as.mcmc(r), prob = 0.90)))
> #colnames(X)[which(apply(sign(ci.prob.90), 1, prod) == 1)]
```

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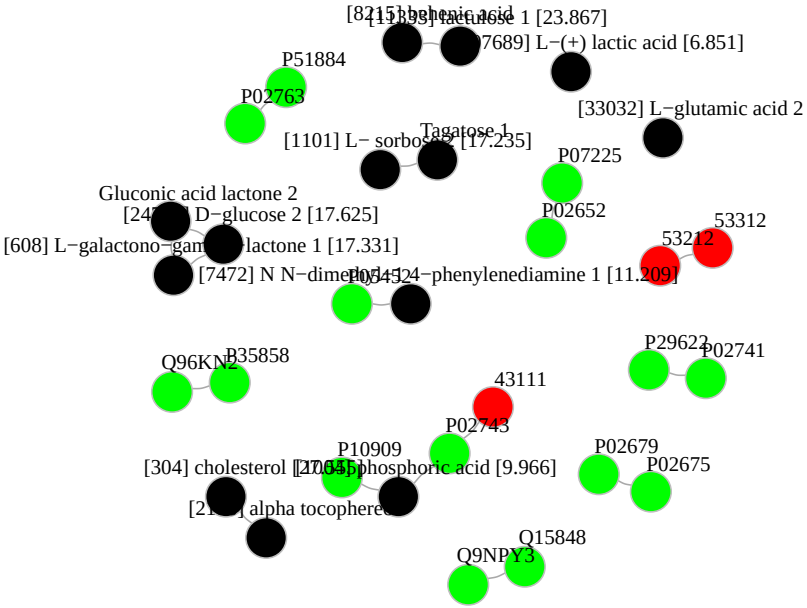
HS-GMRF-sign model

Network for variables selected using a 95% HPD:



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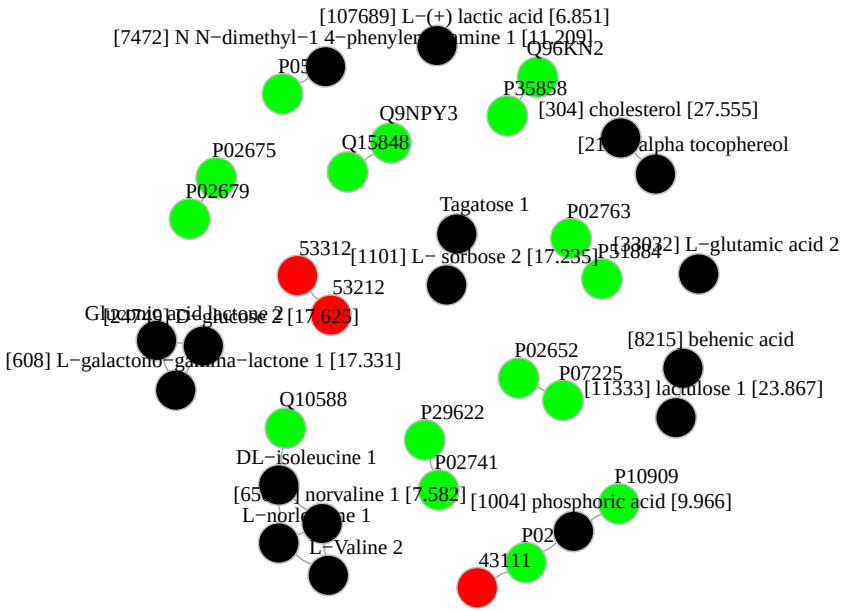
HS-GMRF-sign model

Network for variables selected using a 90% HPD:



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HCC-associated metabolites identified with the proposed approach with 90% HPD

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		Ranking using **iDINGO**		
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3	pyroglutamic acid	ethanolamine	glycine	
4	glycine	creatinine	lactic acid	
5	ethanolamine	tyramine	creatinine	4
6	phenylalanine	mimosine	tyrosine	
7	citric acid	lactic acid	cholesterol	
8	threitol	cholesterol	tyramine	
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Note: Metabolite candidates that appeared in the top-10 ranked lists of all three cohorts are highlighted with the same color.

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Conclusion/Perspectives

Conclusion

- The proposed method allows to integrate *a priori* knowledge on the structure among the predictors through an undirected graph.
- Results in terms of selection and prediction are better than approaches which do not integrate any information or which integrate information at the variable selection indicator level.

Perspectives

- The proposed method may be considered for analyzing multi omic data thanks to the integration of relationships among the covariates.
- To extend to model with a longitudinal response.

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