Revealing the Personal Effects of Nutrition with Mixed-Effect Bayesian Network

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Abstract

This notebook is a supplemential material for the article. The notebook shows in detail how mixed-effect Bayesian network can be used to model the effects of nutrition. The hierarchical structure of the graphical model allows us to study the effects in both typical and personal levels. In addition we show that personal effect variations form clusters of similarly behaving patients. Finally, we show how personal graphical models can be predicted for patients that are held out from the model estimation. This shows that personal differences in nutrional effects do exist, and that they can be detected from repeated observations of food diaries and blood tests.

In this work we propose a Bayesian network as an appealling way to model and predict the effects of nutrition. The Bayesian network are directed graphical models where nodes of the graph are random variables and the edges between the nodes indicate the effects between variables. In the nutritional modelling we assign the amount of nutrients at the person's diet and the indicators of person's well-being as those random variables, and we study the effects between them. The goal is then to find the connections for the graph that most probably describe the correct conditional relationships between nutrients and their effects.

As a practical example, we analyze a dataset from the Sysdimet study (Lankinen et al. 2011) that contains repeated measurements of 17 nutrients, some basic information about patients (gender, medication) and their corresponding blood test results. To ease the graph search, we focus only on two-level, bipartite, graphs where nutrients and personal details are assumed to affect blood tests, and only the magnitude of effect is left to be estimated. As we are interested in the personal variations of these nutritional effects we use a mixed-effect parametrization of Bayesian network (Bae et al. 2016). This allows us to estimate both typical and personal magnitudes of the nutritional effects with a same model.

Formal definition of the nutritional effects model

Let us denote the graph of interconnected nutrients and responses with G. We can then formulate the modeling problem as finding the graph G that is the most probable given the data D

$$P(G|D) \tag{1}$$

By using the Bayes' Rule we can be split this probability into proportions of the data likelihood of the given graph and any prior information we might have about suitable graphs

$$P(G|D) \propto P(D|G)P(G) \tag{2}$$

This turns the problem to finding a graph that is most probable given data. To enforce our assumption of biologically plausible graphs, we set the graph prior $P(G)$ to zero for all other graphs than the previously descibed bipartite graphs with nutrients affecting the bodily responses.

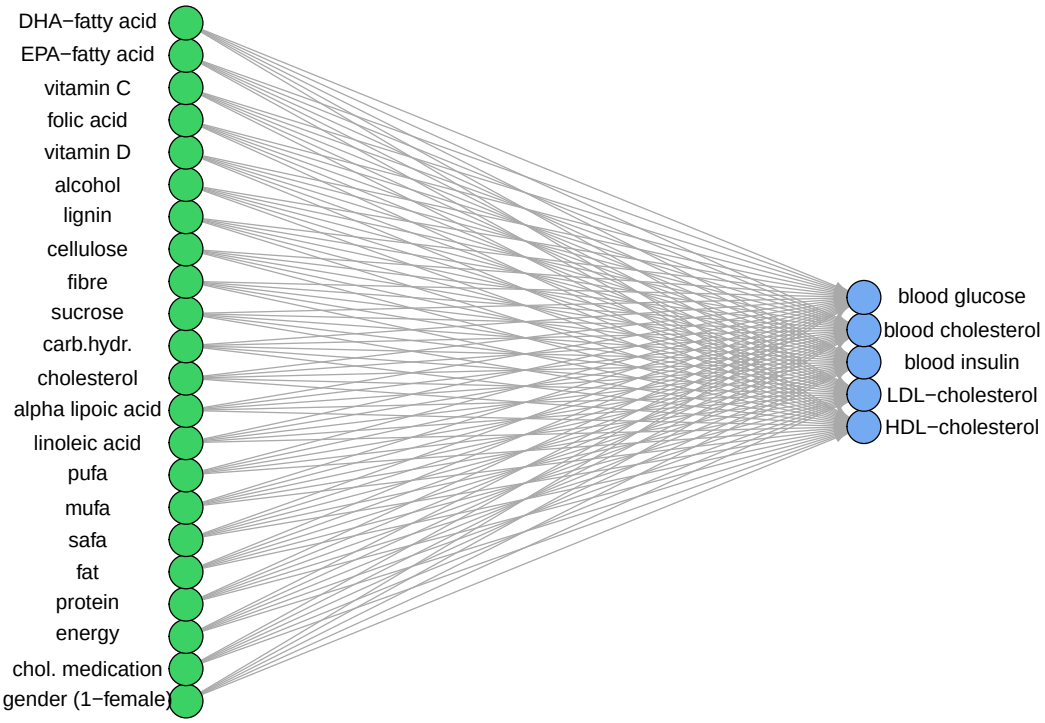
The joint probability of the graph $P(G|D)$ can furthermore factorized into separate local probability distributions (Bae et al. 2016, Koller and Friedman (2009)) by their *Markov blankets*. Hierarchical mixed-effect estimation allows us to study the distributions in both typical and personal levels.

Hierarchical estimation of the local distributions

The joint probability distribution of the graph is factorized into separate distributions. We assume that the blood test random variables Y_i are affected by a linear combination of the nutrient variables $pa(Y_i)$. The set of parameters describing this effect, ϕ_i, can be split into typical β and personal b parts. We assume that the actual data denoted by the random variables follows distributions from the exponential family and we can use some link function to use this linear predictor.

$$\begin{aligned} P(D|G)P(G) &= \prod_{i=1}^{v} P(D|G_i)P(G_i) \\ &= \prod_{i=1}^{v} P(Y_i|pa(Y_i), \phi_i)P(G_i) \\ &= \prod_{i=1}^{v} EXPFAM(Y_i|pa(Y_i)\beta_i + pa_Z(Y_i)b_i, \sigma^2)P(G_i) \end{aligned} \tag{3}$$

Note that while this formulation generalizes to graphs with multiple levels, we have a prior assumption, $P(G)$, that the structure of our dataset is a bipartite graph.



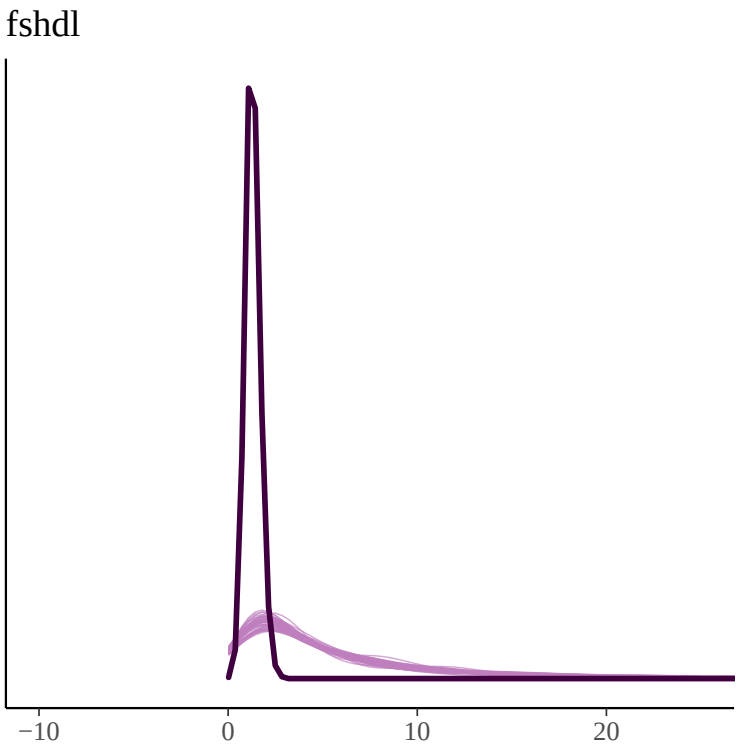
We assume a connection from every nutrient and personal information to every blood test value at the dataset.

The model search is then focused on to estimating optimal coefficients β and b that we use to define the strength of the connection. It is also important to find correct probability distributions for the random variables.

Our starting assumption is that both nutrients and the blood test values are normally distributed. This assumption may be naive as it allows the blood tests to have negative values. We normalize all the input values to same scale, so that the estimated regression coefficients can be used as a indicators of connection strenght.

```
sysdimet_normal <- mebn.bipartite_model(reaction_graph = initial_graph,
                                        inputdata = sysdimet,
                                        predictor_columns = assumedpredictors,
                                        assumed_targets = assumedtargets,
                                        group_column = "SUBJECT_ID",
                                        local_estimation = mebn.sampling,
                                        local_model_cache = "models/BLMM_normal",
                                        stan_model_file = "mebn/BLMM_normal.stan",
                                        normalize_values = TRUE)
```

We can assess the model fit by plotting the posterior predictive distributions (PPC) over the distributions of the true blood test values. As expected, the Gaussian random variables are not fitting well.

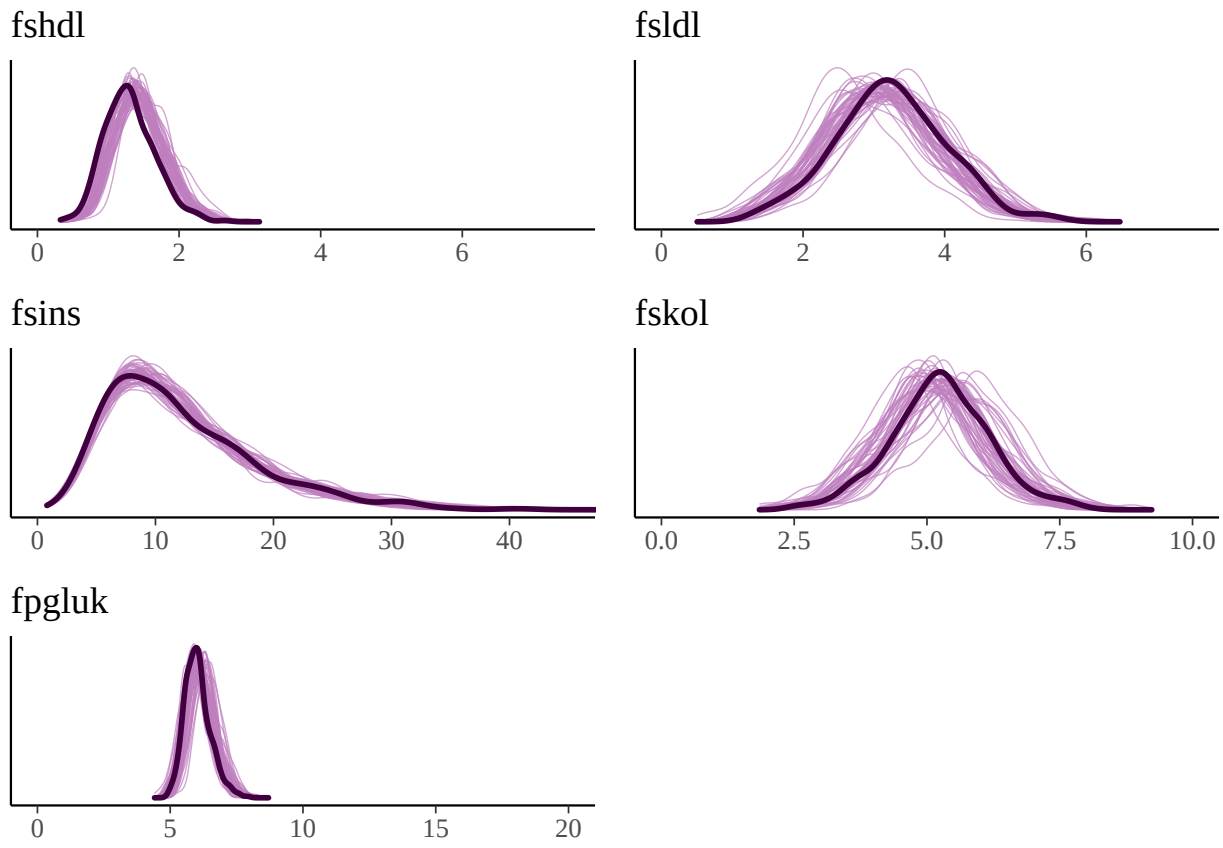


Developing the model beyond normal distributions

More realistic probability distribution for blood test values would be Log-Normal or Gamma distributions (Limpert 2011). They both allow only positive values and model better the right tail of individual larger values. For further development, we choose Gamma distribution with identity link function. This is important as it keeps the regression coefficients of the nutrients on the same absolute scale than with Normal models. The regression coefficients are used as weights of the edges at the Bayesian network and they all should be on the same scale regardless of the random variables' distribution.

```
initial_gamma_graph <- mebn.new_graph_with_randomvariables(datadesc)

sysdimet_gamma <- mebn.bipartite_model(reaction_graph = initial_gamma_graph,
                                       inputdata = sysdimet,
                                       predictor_columns = assumedpredictors,
                                       assumed_targets = assumedtargets,
                                       group_column = "SUBJECT_ID",
                                       local_estimation = mebn.sampling,
                                       local_model_cache = "models/BLMM_gamma/hierarchical_idlink",
                                       stan_model_file = "mebn/BLMM_gamma_hierarchical.stan",
                                       normalize_values = TRUE)
```

The visual comparison of the true and estimated distributions of blood test variables shows that Gamma distribution follows the true distributions quite well. The estimate has lots of variance and we should focus on that next.



Graph probability approximation with LOO

Besides the visual inspection, we can also compare the models using LOO-PSIS information criteria (Vehtari, Gelman, and Gabry (2017)). It uses log probability that is calculated as part of the Stan models. We can approximate the probability of the whole graph by summing over the expected log predictive densities (ELPD) of every distict local distribution at the graph.

This shows how the local distributions with Normal and Gamma distribution compare to each other

```
normal_vs_gamma <- mebn.LOO_comparison(assumedtargets, "BLMM_normal", "BLMM_gamma/hierarchical_idlink")
```

distribution	BLMM_normal	BLMM_gamma/hierarchical_idlink
fshdl	-801.238 (3.928)	-895.79 (64.318)
fsldl	-3149.55 (45.452)	-2039.735 (141.853)
fsins	-1272.615 (25.446)	-1063.643 (15.302)
fskol	-5469.744 (66.412)	-974.159 (50.588)
fpgluk	-27242.896 (167.91)	-469.038 (27.527)

As ELPD of the gamma model is higher, we should choose that for further development.

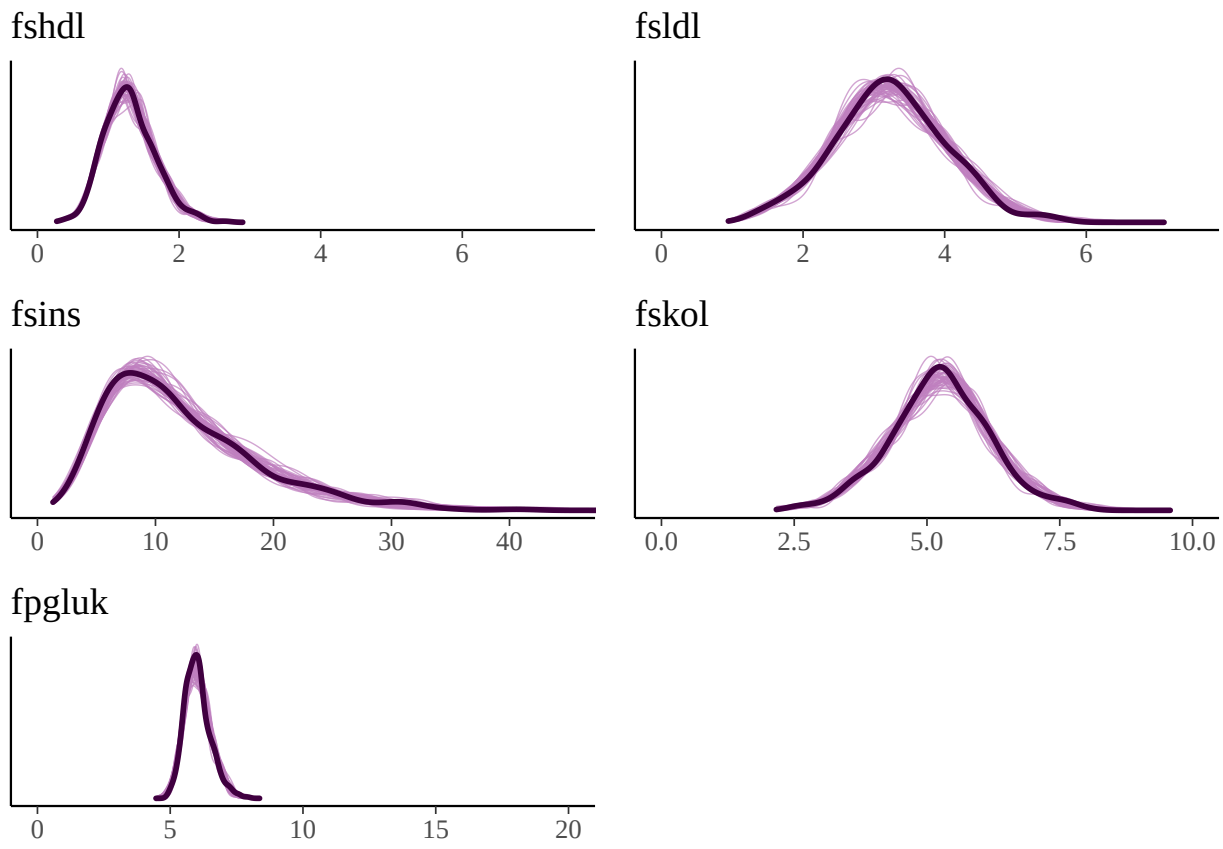
Modeling the varying response time with an autocorrelation structure

In the dataset the observations from patients' food diaries and blood tests have one week response time. This might not be optimal time for all the responses and the successive observations might be correlated. For modeling the correlated residuals, we add an autocorrelation structure to the model. As there are only four observations from each patient, we consider only one previous residual for each observation.

In Stan model this AR(1) structure is calculated as follows

```
...
    // - calculate residuals
    e[n] = Y[n] - mu[n];

    // - estimate autoregression coefficient for observations of one patient
    if (group_size > 1)
      mu[n] += e[n-1] * ar1;

...
```

The autocorrelation structure seems to decrease the variance of the model



Numerically the difference is also significant between models with AR(0) and AR(1)

```
ar0_vs_ar1 <- mebn.LOO_comparison(assumedtargets, "BLMM_gamma/hierarchical_idlink", "BLMM_gamma/ar1")
```

distribution	BLMM_gamma/hierarchical_idlink	BLMM_gamma/ar1
fshdl	-895.79 (64.318)	204.102 (16.277)
fsldl	-2039.735 (141.853)	-171.428 (16.463)
fsins	-1063.643 (15.302)	-1070.504 (15.523)
fskol	-974.159 (50.588)	-308.398 (16.388)
fpgluk	-469.038 (27.527)	-186.111 (19.1)

It is interesting also to compare the AR(1) coefficients of different local distributions at the graph. For HDL cholesterol (fshdl), combined cholesterol (fskol) and the blood glucose (fpgluk) the positive AR(1) coefficient indicates that the effect of nutrition spans longer than one week

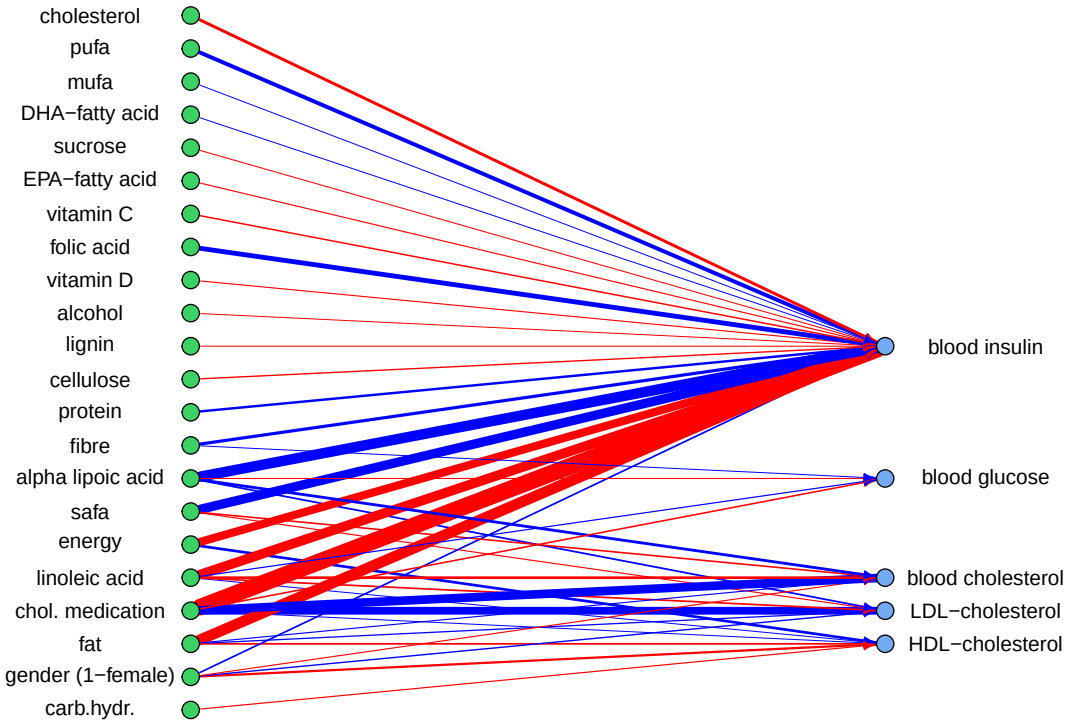
```
ar1_comparison <- mebn.AR_comparison(assumedtargets, "BLMM_gamma/ar1")
```

distribution	AR(1)	CI-10%	CI-90%
fshdl	0.08869	-0.07473	0.25418
fsldl	0.00874	-0.15134	0.17924
fsins	-0.00968	-0.15569	0.13973
fskol	0.12575	-0.04315	0.30844
fpgluk	0.10030	-0.03282	0.24079

Typical effects of nutrition, and variance from the typical effects

We have now reached a reasonable good fit for the local distributions of the Bayesian network. Our code has extracted a graphical model from these posterior distributions of random variables and parameters. The graph consists mean values of the posteriors and also their credible intervals. This is a lighter data structure for further analysis and allows also graph operations besides the regression modeling.

Besides the random variables, the graph also includes the regression coefficients β and b that denote the typical and personal magnitudes of the effects for different nutrients. For better overview, let us plot the graph of typical nutritional effects. This visualization shows typical coefficients β as weight of the connection between blood test and nutrients at diet affecting it. For clarity, the visualization only shows 15 principal components explaining the variance of each blood test



The effects with most personal variance

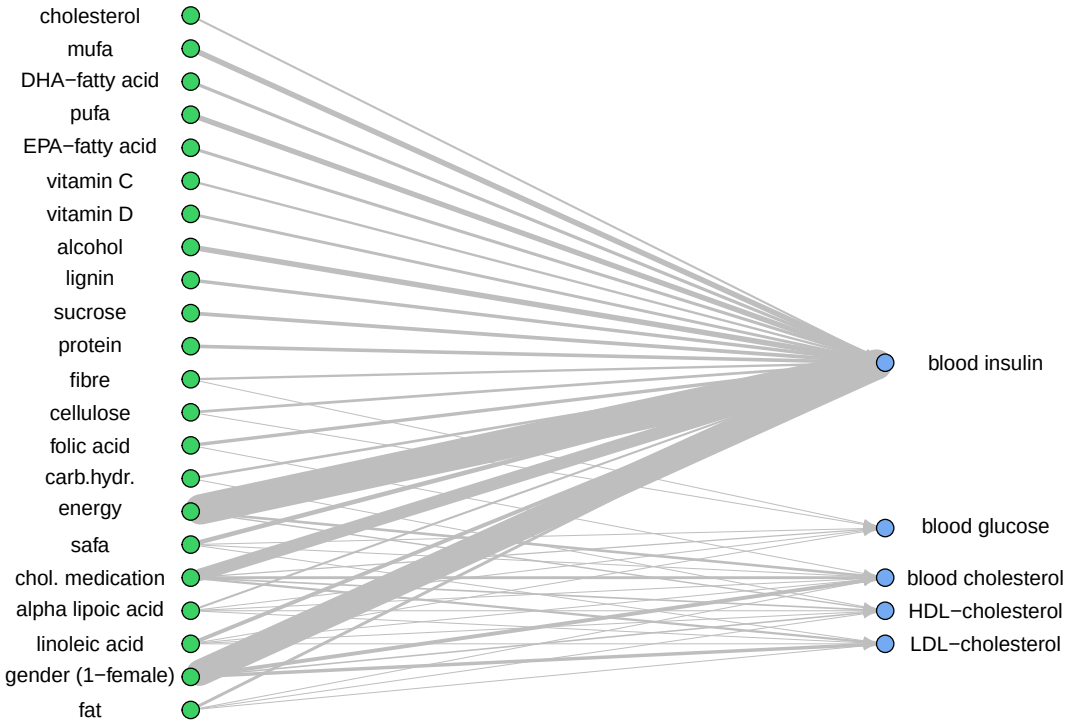
Beside the typical effects, our main interest lies on the personal effects b and their variances σ_b. If there is a large variance for the personal effect it means that there exists personal differences in reaction types. These differences are our main interest to find.

When this dataset is arranged as a bipartite graph, there are 22*5=110 possible effects between nutrients and blood tests. For finding the most interesting effects with most personal variance, we extract and sort b_sigma-hyperparameters from the graph.

	effect	variance	CI-10%	CI-90%
47	energy -> blood insulin	3.88391	1.39840	6.25608
45	gender (1-female) -> blood insulin	3.37135	1.89307	4.74329
46	chol. medication -> blood insulin	1.59519	0.26960	3.14330
51	mufa -> blood insulin	0.70719	0.13930	1.31536
61	alcohol -> blood insulin	0.70027	0.15894	1.21128
52	pufa -> blood insulin	0.68871	0.12248	1.30574
50	safa -> blood insulin	0.58117	0.09570	1.19980
67	gender (1-female) -> blood cholesterol	0.50325	0.28243	0.70513
53	linoleic acid -> blood insulin	0.50259	0.08422	0.99303
57	sucrose -> blood insulin	0.48189	0.07653	0.96654
48	protein -> blood insulin	0.45802	0.06947	0.94827
23	gender (1-female) -> LDL-cholesterol	0.44292	0.27573	0.60618
60	lignin -> blood insulin	0.44076	0.07831	0.87382
63	folic acid -> blood insulin	0.43577	0.07226	0.88768
66	DHA-fatty acid -> blood insulin	0.42098	0.07120	0.84157
65	EPA-fatty acid -> blood insulin	0.40134	0.06641	0.79980
49	fat -> blood insulin	0.38449	0.06806	0.77410
62	vitamin D -> blood insulin	0.37727	0.05959	0.76792
68	chol. medication -> blood cholesterol	0.36859	0.08022	0.66050
59	cellulose -> blood insulin	0.34831	0.05924	0.69903

These are the effect with most difference between patients. Let us the examine closer those of the effects that have most probable variance over 0.30 and plot them as a graph

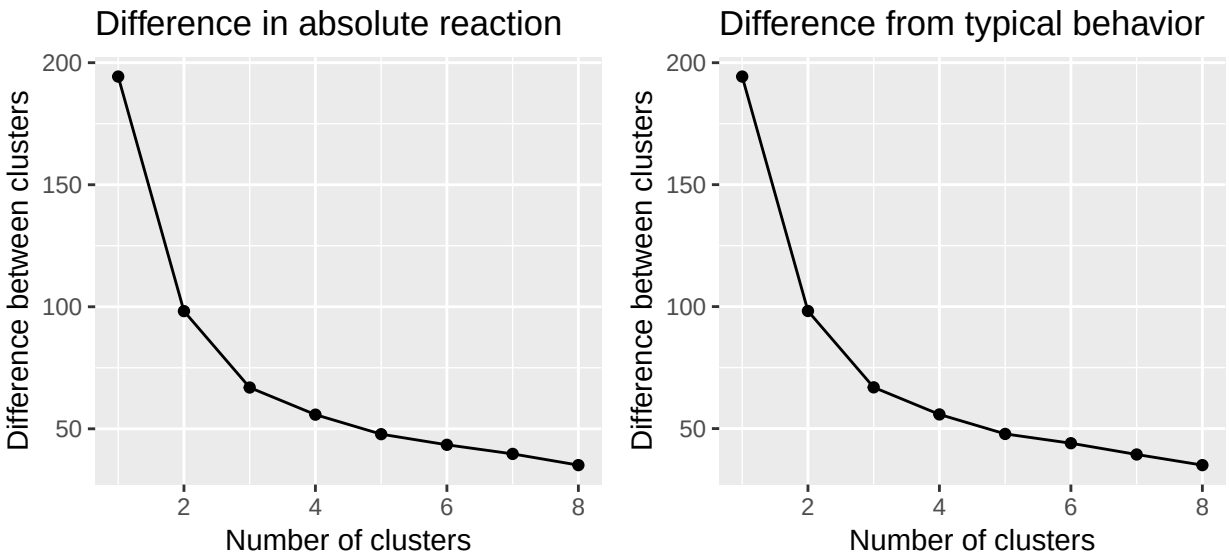
```
effects_with_most_variance <- ordered_personal_variance[ordered_personal_variance$variance >= 0.30,]
number_of_varying_effects <- nrow(effects_with_most_variance)

mebn.plot_personal_variations(sysdimet_gamma_ar1, number_of_varying_effects)
```



Finding the clusters of personal reaction types

Although there are personal differences, it is likely that everyone is not behaving uniquely but there might exist similar groups of behavior. We can analyze personal differences in two ways. We can look the absolute magnitudes of effects and we can also look how persons differ from typical behavior or mean of the effect.

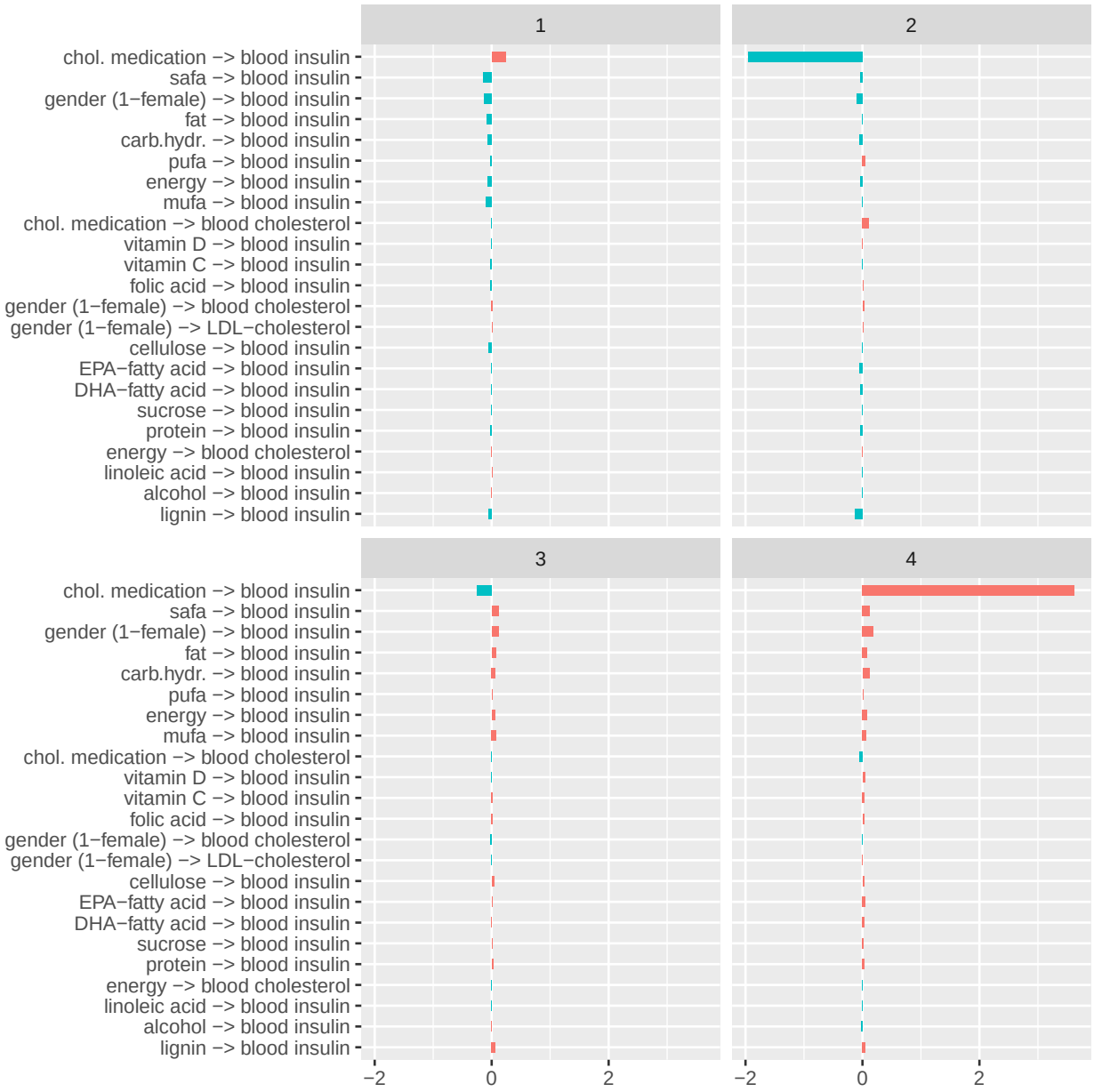
We can now take the personal estimations of the effects and see, if they form clusters



By looking previous diagram we see that there are four clearly identifiable groups between patients.

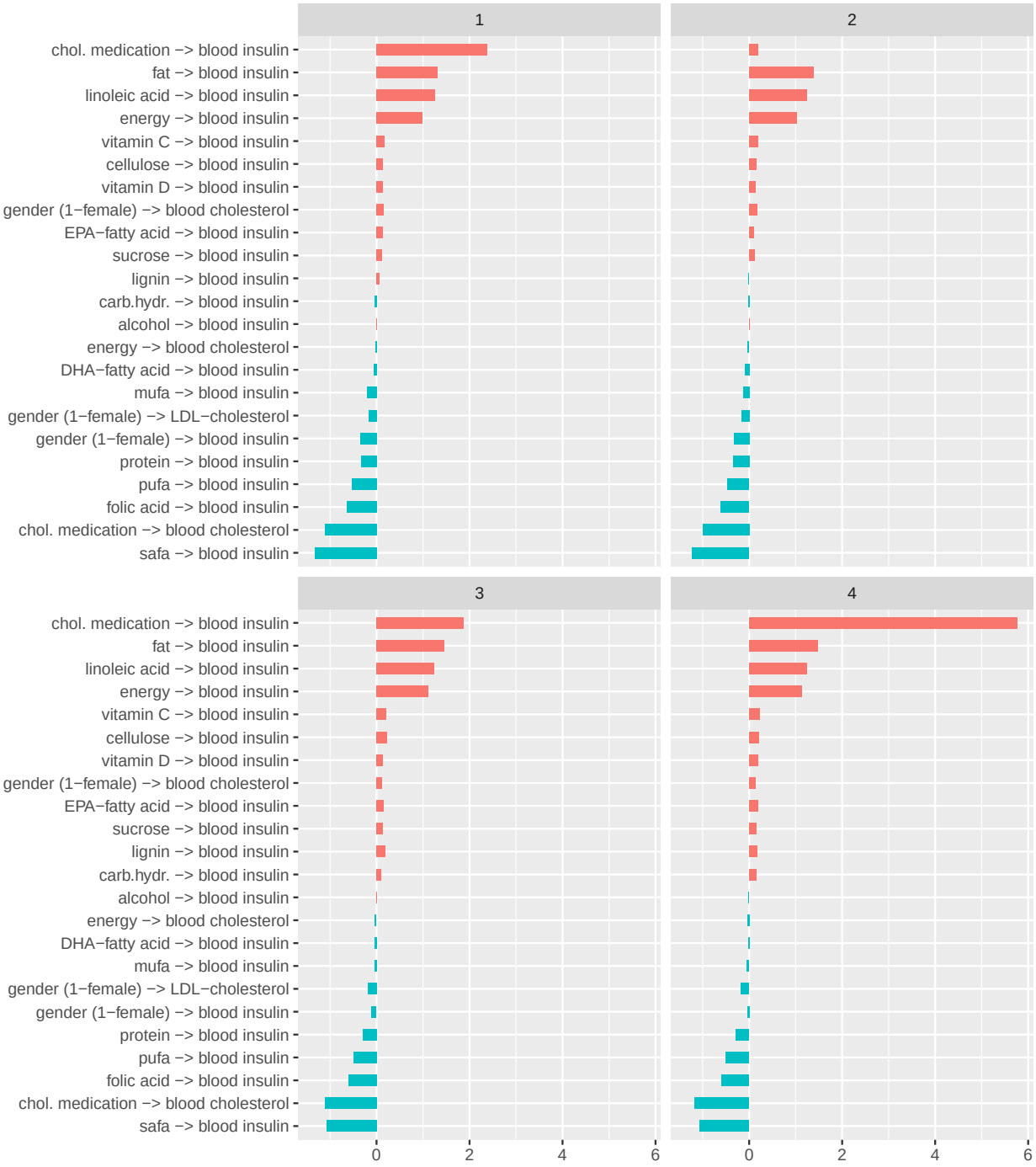
The effect of cholesterol medication

At this plot, zero of X-axis denotes a typical behaviour of that particular reaction, and blue and red bars denote a deviation from this typical mean.



Cholesterol medication seems to dominate the clusters. There are patients for who cholesterol medication raises the blood insulin levels more than on average and for other group the raise is less than on average.

Let's see how the clustering shows with absolute effects rather than difference from mean. Note that these are not the greatest effects, but those with most personal variance.



By looking at the absolute effect of the cholesterol medication it seems that there separetes two groups where one it is a significant factor in explaining blood insulin level, and other group where it does not play virtually any role. But does these patients even take cholesterol medications? Let's create a cross tabulation of observations to explore this effect more closely.

	1	**2**	**3**	**4**
No medication	156	0	152	0
Chol. med.	20	36	32	28

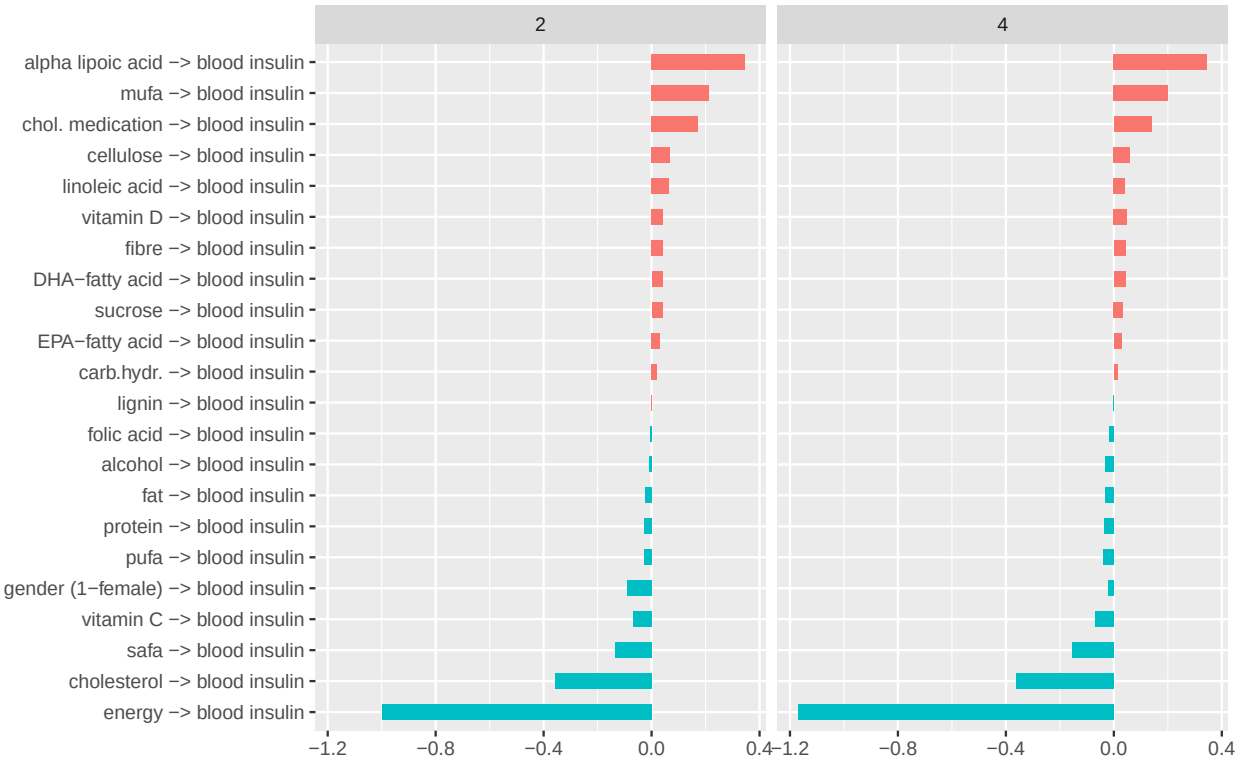
This indicates that patients in clusters 2 and 4 are indeed taking cholesterol medication.

The average blood insulin levels in these clusters are

cluster	average blood insulin
1	8.419886
2	8.430556
3	14.750815
4	23.110714

There are 9 (=36/4) and 7 (=28/4) patients in clusters 2 and 4 who are taking cholesterol medication. For patients in the cluster 4 the average insulin level is the medication seems to rise the insulin level quite much, but for patients in the cluster 2 not much at all.

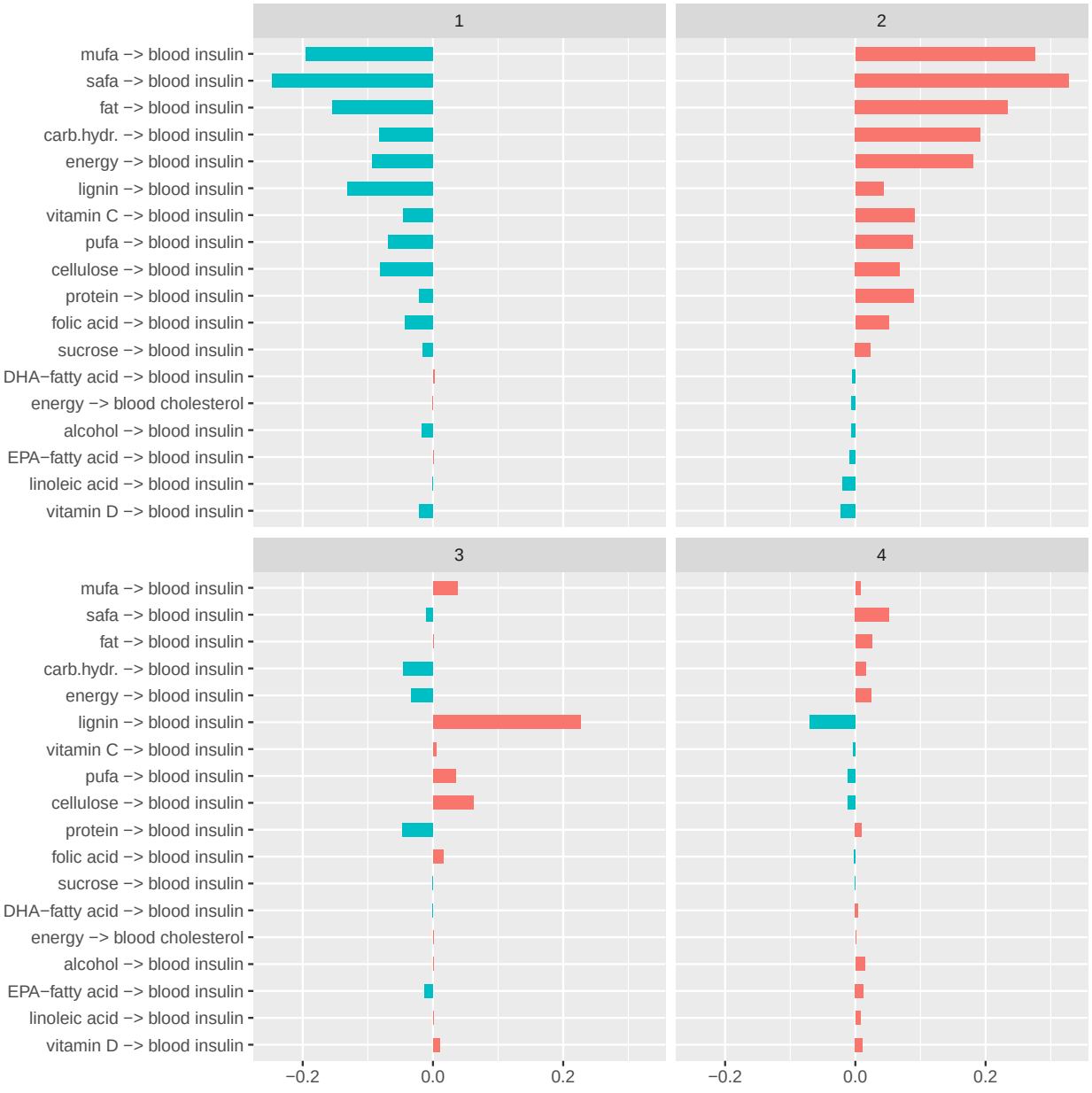
Let's try to confirm this finding by visualizing the components of insulin variance.

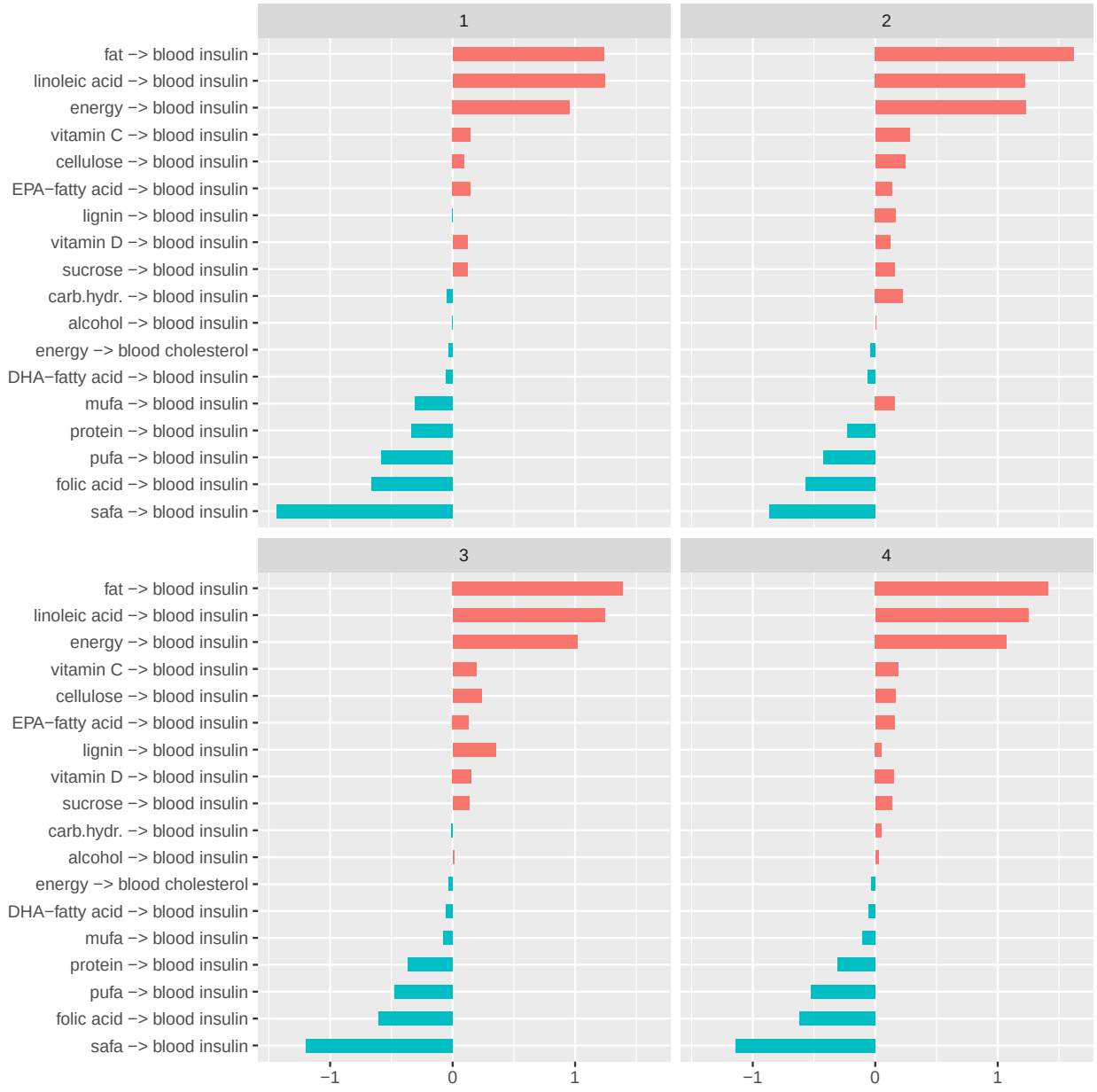


So, based on this we have an evidence that there is group on patients in this dataset who has significantly larger blood insulin values on average and a major component affecting the raise is cholesterol medication.

Clustering with nutritional effects only

Both gender and cholesterol medication are unchanging factors at the dataset. Let us next remove those from clustering features and see how the clusters form based on nutritional effects only.


1
2
3
4
mufa −> blood insulin
safa −> blood insulin
fat −> blood insulin
carb.hydr. −> blood insulin
energy −> blood insulin
lignin −> blood insulin
vitamin C −> blood insulin
pufa −> blood insulin
cellulose −> blood insulin
protein −> blood insulin
folic acid −> blood insulin
sucrose −> blood insulin
DHA−fatty acid −> blood insulin
energy −> blood cholesterol
alcohol −> blood insulin
EPA−fatty acid −> blood insulin
linoleic acid −> blood insulin
vitamin D −> blood insulin
−0.2
0.0
0.2



In clusters 1 and 2 there are patients whose blood insulin levels react on lower and on higher than average. One interesting difference is lignin's effect to the blood insulin.

Predicting the personal reaction type for new patients

Finally, we can pick one the previously found reaction type clusters and hold aside the data for few of these patients. The goal would be then to use our model to predict the blood test values for this test group by their diet. This also reveals their personal reaction type for nutrition. We can compare this prediction to the true blood test values at dataset and also to the previous estimates from the whole sample population.

For testing, we sample a holdout set of patients overall the dataset. We then train a model without this holdout set and test how accurately we can place the predicted reaction types in previously found clusters. Note that we don't know the true reaction types for these patients. This makes absolute testing of prediction

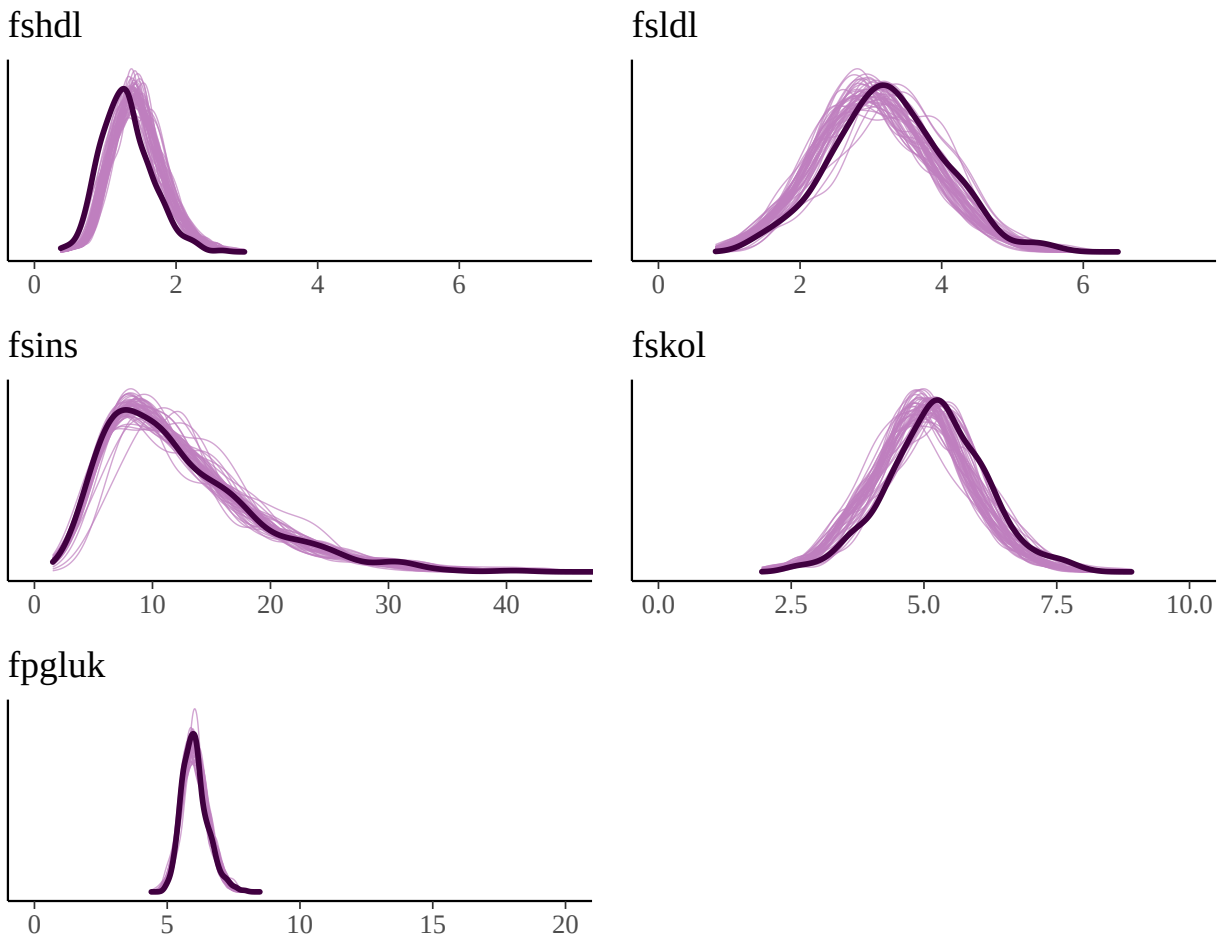
performance impossible, but in this way we can see at least if the prediction is consistent with analysis of the whole dataset. We know the previous cluster assiments of these holdout patients.

The predictive ability of the model might be reduced by overfitting to small nuances of the whole dataset. To overcome the possible overfitting, we apply the Finnish horseshoe, a shrinkage prior, on regression coefficients. It allows specifying a prior knowledge, or at least an educated guess, about the number of significant predictors for a target. Here we guess that one third of the nutrients might be relevant for any given blood test, and apply following parameters for the shrinkage

```
shrinkage_parameters <- within(list(),
{
    scale_icept  <- 1         # prior std for the intercept
    scale_global <- 0.01825   # scale for the half-t prior for tau:
                              # ((p0=6) / (D=22-6)) * (sigma / sqrt(n=106*4))
    nu_global    <- 1         # degrees of freedom for the half-t priors for tau
    nu_local     <- 1         # degrees of freedom for the half-t priors for lambdas
    slab_scale   <- 1         # slab scale for the regularized horseshoe
    slab_df      <- 1         # slab degrees of freedom for the regularized horseshoe
})
```

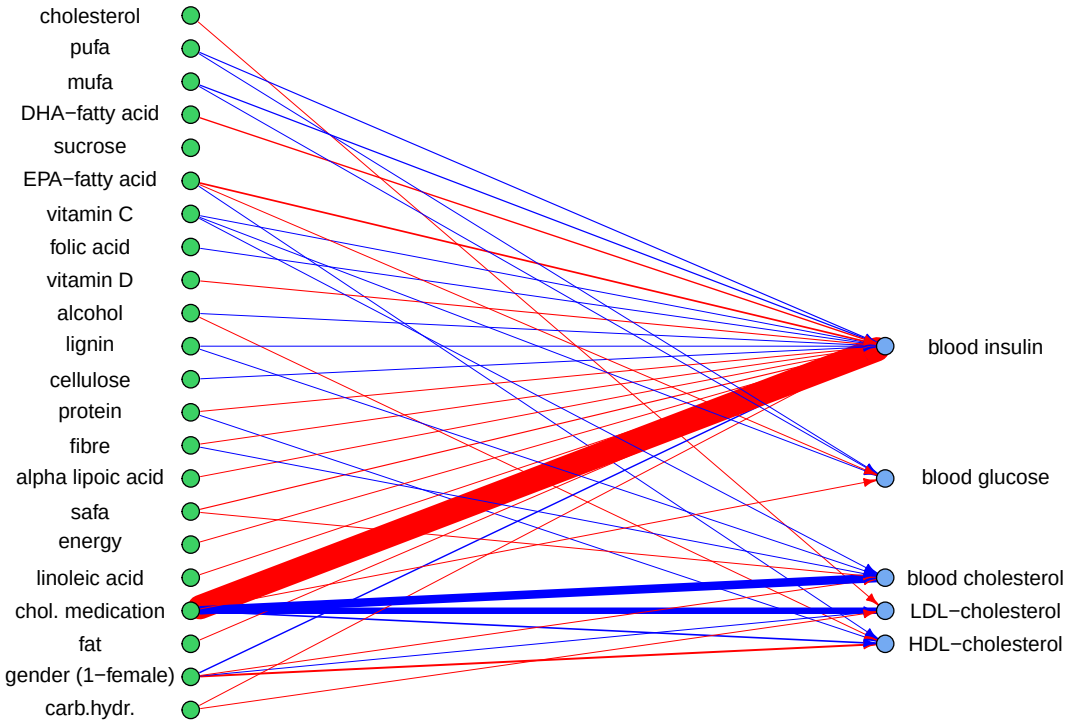
Next we fit the previous model with the Finnish horseshoe added. Besides the shrinkage parameters, we provide now the data in two sets: input data for estimation and target data to hold out for prediction.

```
initial_graph <- mebn.new_graph_with_randomvariables(datadesc)
sysdimet_gamma_ar1_rhs_pred <- mebn.bipartite_model(reaction_graph = initial_graph,
                                    inputdata = sysdimet,
                                    targetdata = holdout_index,
                                    predictor_columns = assumedpredictors,
                                    assumed_targets = assumedtargets,
                                    group_column = "SUBJECT_ID",
                                    local_estimation = mebn.sampling,
                                    local_model_cache = paste0("models/BLMM_gamma/ar1_rhs_effpred"),
                                    stan_model_file = "mebn/BLMM_gamma_ar1_rhs_effpred.stan",
                                    reg_params = shrinkage_parameters,
                                    normalize_values = TRUE)

write.graph(sysdimet_gamma_ar1_rhs_pred, "sysdimet_gamma_ar1_rhs_pred.graphml", "graphml")
```

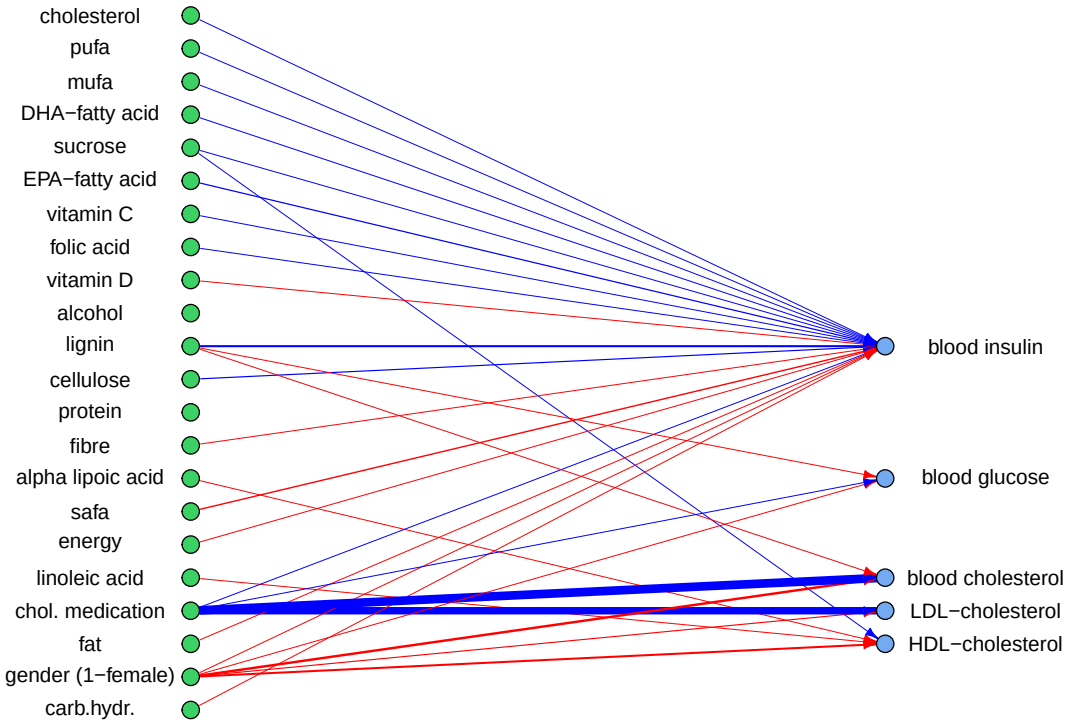


We can then compare the visualizations of the personal reaction graphs. The effect of cholesterol medication is most significant difference, but other differences exist as well.

Subject 94

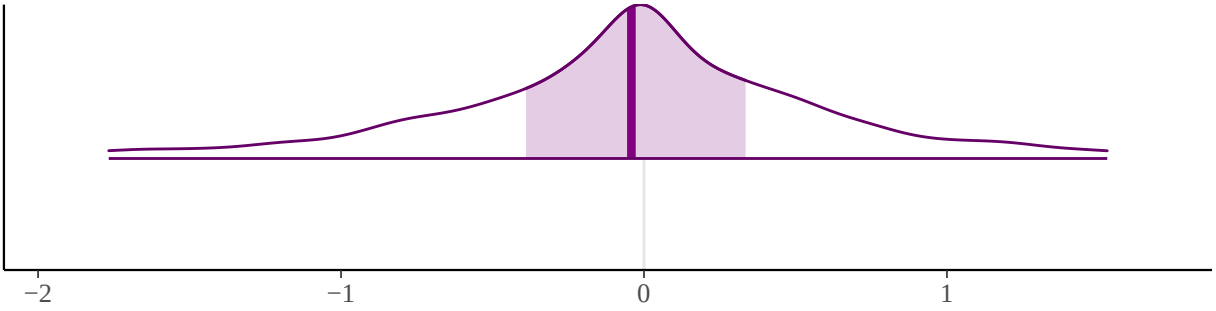

cholesterol
pufa
mufa
DHA−fatty acid
sucrose
EPA−fatty acid
vitamin C
folic acid
vitamin D
alcohol
lignin
cellulose
protein
fibre
alpha lipoic acid
safa
energy
linoleic acid
chol. medication
fat
gender (1−female)
carb.hydr.
blood insulin
blood glucose
blood cholesterol
LDL−cholesterol
HDL−cholesterol

Subject 37

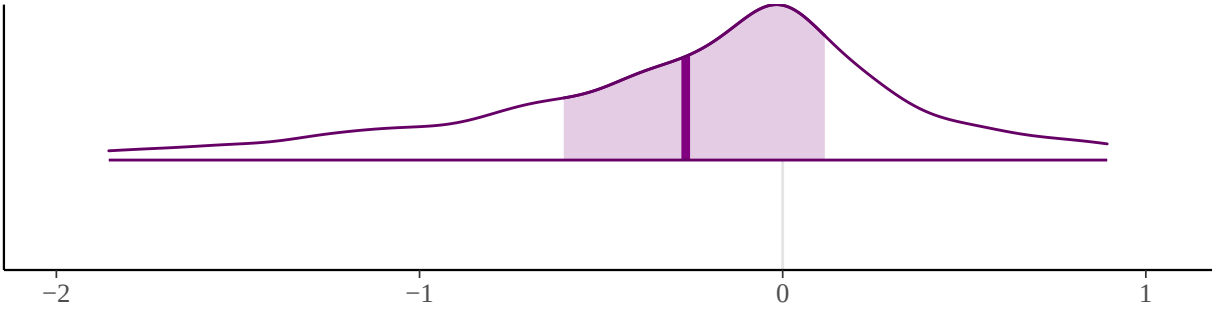


The graph visualizations show only the means of the effect magnitudes. We can also go deeper and inspect the posterior predictive distributions of the effects. Here are the effects of cholesterol medication and lignin to the blood insulin. The outline of the plot shows 95% credible interval and the dark band shows 50% credible interval.

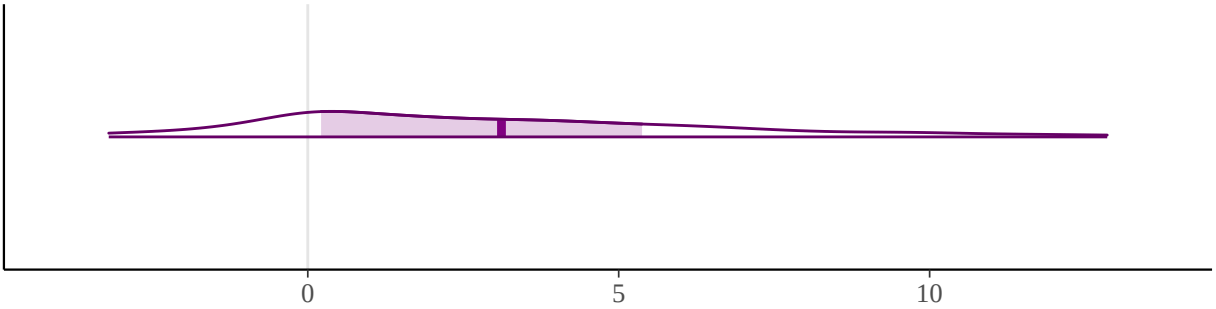
lignin −> fsins, subject 94



lignin −> fsins, subject 37



chol.med. −> fsins, subject 94



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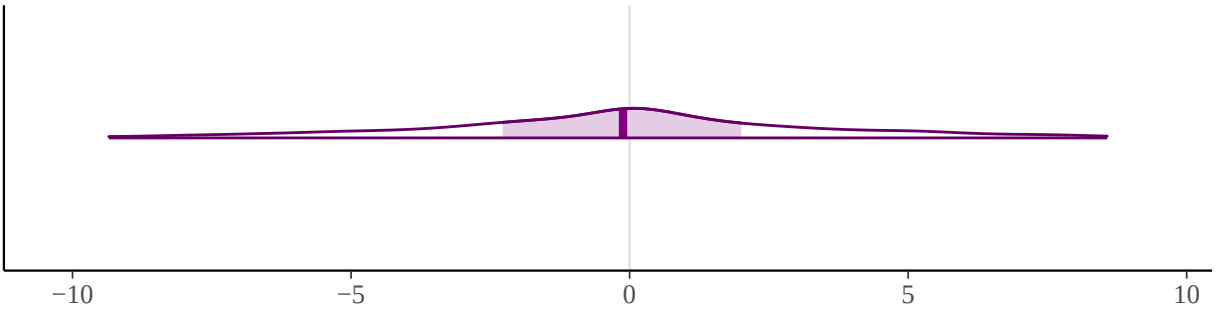

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