Stable Graphical Model Estimation with Random Forests for Discrete, Continuous, and Mixed Variables

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Abstract

A conditional independence graph is a concise representation of pairwise conditional independence among many variables. Graphical Random Forests (GRaFo) are a novel method for estimating pairwise conditional independence relationships among mixed-type, i.e. continuous and discrete, variables. The number of edges is a tuning parameter in any graphical model estimator and there is no obvious number that constitutes a good choice. Stability Selection helps choosing this parameter with respect to a bound on the expected number of false positives (error control).

The performance of GRaFo is evaluated and compared with various other methods for p = 50, 100, and 200 possibly mixed-type variables while sample size is n = 100 (n = 500 for maximum like-lihood). Furthermore, GRaFo is applied to data from the Swiss Health Survey in order to evaluate how well it can reproduce the interconnection of functional health components, personal, and environmental factors, as hypothesized by the World Health Organization's International Classification of Functioning, Disability and Health (ICF). Finally, GRaFo is used to identify risk factors which may be associated with adverse neurodevelopment of children who suffer from trisomy 21 and experienced open-heart surgery.

GRaFo performs well with mixed data and thanks to Stability Selection

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it provides an error control mechanism for false positive selection.

Keywords: Graphical Model, High Dimensions, LASSO, Mixed Data, Random Forests, Stability Selection

1 1. Introduction

In many problems one is not confined to one response and a set of pre-2 defined predictors. In turn, the interest is often in the association structure 3 of a whole set of p variables, i.e. asking whether two variables are independent conditional on the remaining p-2 variables. A conditional independence 5 graph (CIG) is a concise representation of such pairwise conditional indepen-6 dence among many possibly mixed, i.e. continuous and discrete, variables. In CIGs, variables appear as nodes, whereas the presence (absence) of an edge among two nodes represents their dependence (independence) conditional on a all other variables. Applications include among many others also the study 10 of functional health (Strobl et al., 2009; Kalisch et al., 2010; Reinhardt et al., 11 2011). 12

We largely focus on the high-dimensional case where the number of vari-13 ables (nodes in the graph) p may be larger than sample size n. A popu-14 lar approach to graphical modeling is based on the Least Absolute Shrink-15 age and Selection Operator (LASSO; Tibshirani, 1996): see Meinshausen 16 and Bühlmann (2006) or Friedman et al. (2008) for the Gaussian case and 17 Ravikumar et al. (2010) for the binary case. However, empirical data of-18 ten involve both discrete and continuous variables. Conditional Gaussian 19 distributions were suggested to model such mixed-type data with maximum 20 likelihood inference (Lauritzen and Wermuth, 1989), but no corresponding 21 high-dimensional method has been suggested yet. Dichotomization, though 22 always applicable, comes at the cost of lost information (MacCallum et al., 23 2002).24

Tree-based methods are easy to use and accurate for dealing with mixed-25 type data (Breiman et al., 1984). Random Forests (Breiman, 2001) evalu-26 ate an ensemble of trees often resulting in notably improved performance 27 compared to a single tree (see also Amit and Geman, 1997). Furthermore, 28 permutation importance in Random Forests allows to rank the relevance of 29 predictors for one specific response. However, Random Forests have 30 also been criticized to perform possibly biased variable selection. 31 We thus also consider Conditional Forests (Strobl et al., 2007) and 32

³³ conditional variable importance (Strobl et al., 2008), which have
³⁴ been suggested to overcome this behavior.

In general, the definition of **both the conditional and marginal** per-35 mutation importance differ for discrete and continuous responses. Thus. 36 ranking permutation importances across responses of mixed-type is less ob-37 vious. However, such ranking is essential to derive a network of the most 38 relevant dependencies. Stability Selection proposed by Meinshausen and 39 Bühlmann (2010) is one possible framework to rank the edges in the CIG 40 across different types of variables. In addition, it allows to specify an up-41 per bound on the expected number of false positives, i.e. the falsely selected 42 edges, and thus provides a means of error control. 43

We combine Random Forests estimation with appropriate ranking among 44 mixed-type variables and error control from Stability Selection. We refer to 45 the new method as Graphical Random Forests (GRaFo). The specific aims 46 of the paper are a) to evaluate and compare the performance of GRaFo 47 with Stable LASSO (StabLASSO) and Stable Conditional Forests 48 (StabcForests), which are LASSO- and conditional forest-based al-49 ternatives, and regular maximum likelihood (ML) estimation across 50 various simulated settings comprising different distributions, interactions, 51 and nonlinear associations for p = 50, 100, and 200 possibly mixed-type 52 variables while sample size is n = 100 (n = 500 for ML), b) to apply GRaFo 53 to data from the Swiss Health Survey (SHS) to evaluate the interconnec-54 tion of functional health components, personal, and environmental factors, 55 as hypothesized by the World Health Organization's (WHO) International 56 Classification of Functioning, Disability and Health (ICF), and c) to use 57 GRaFo to identify risk factors associated with adverse neurodevelopment in 58 children with trisomy 21 after open-heart surgery and more generally to 59 assess the plausibility of the suggested associations. 60

⁶¹ 2. Graphical Modeling Based on Regression-Type Methods

62 2.1. Conditional Independence Graphs

Let $\mathbf{X} = \{X_1, \ldots, X_p\}$ be a set of (possibly) mixed-type random variables. The associated conditional independence graph of \mathbf{X} is the undirected graph $G_{\text{CIG}} = (\mathcal{V}, \mathcal{E}(G_{\text{CIG}}))$, where the nodes in \mathcal{V} correspond to the p variables in \mathbf{X} . The edges represent the pairwise Markov property, i.e. $i - j \notin \mathcal{E}(G_{\text{CIG}})$ if and only if $X_j \perp X_i | \mathbf{X} \setminus \{X_j, X_i\}$. For a rigorous introduction to graphical models, see, for example, the monographs by Whittaker (1990) or Lauritzen
(1996).

We will now show that the pairwise Markov property can, under certain conditions, be inferred from conditional mean estimation.

Theorem 1. Assume that, for all j = 1, ..., p, the conditional distribution of X_j given $\{X_h; h \neq j\}$ is depending on any realization $\{x_h; h \neq j\}$ only through the conditional mean function

$$m_j(\{x_h; h \neq j\}) = \mathbb{E}[X_j | \{x_h; h \neq j\}],$$

that is:

$$\mathbb{P}[X_j \le x_j | \{x_h; h \ne j\}] = F_j(x_j | m_j(\{x_h; h \ne j\})), \tag{A}$$

where $F_j(\cdot|m)$ is a cumulative distribution function for all $m \in \mathbb{R}$ (or $m \in \mathbb{R}^d$ if X_j is d-dimensional). (Thereby, we assume that the conditional mean exists). Then

$$X_j \perp X_i | \{X_h; h \neq j, i\}$$

if and only if

$$m_j(\{x_h; h \neq j\}) = m_j(\{x_h; h \neq j, i\})$$

⁷² does not depend on x_i , for all $\{x_h; h \neq j\}$.

A proof is given in Section 8. Assumption (A) trivially holds for a Bernoulli random variable X_j :

$$\mathbb{P}[X_j = 1 | \{x_h; h \neq j\}] = \mathbb{E}[X_j | \{x_h; h \neq j\}] = m_j(\{x_h; h \neq j\}).$$

Analogously, for a multinomial random variable X_j with C levels, the probability that X_j takes the level $r \in \{1, \ldots, C\}$ can be expressed via a Bernoulli variable $X_j^{(r)}$ with

$$\mathbb{P}[X_j^{(r)} = 1 | \{x_h; h \neq j\}] = \mathbb{E}[X_j^{(r)} | \{x_h; h \neq j\}] = m_j(\{x_h; h \neq j\}).$$

Hence, (A) holds. Moreover, if $(X_1, \ldots, X_p) \sim \mathcal{N}_p(\mathbf{0}, \Sigma)$, then (A) holds as well (see for example Lauritzen, 1996). However, for the Conditional Gaussian distribution (or CG distribution, see e.g. Lauritzen, 1996), we need to

require for (A) that the variance is fixed and is not depending on the variables we condition on. For example, let $X_1 \sim \mathcal{B}(1,\pi)$ be Bernoulli distributed and let

$$X_2|X_1 \sim \begin{cases} \mathcal{N}(\mu_1, \sigma_1^2), \text{ if } X_1 = 1\\ \mathcal{N}(\mu_2, \sigma_2^2), \text{ if } X_1 = 0 \end{cases}$$
, where $\sigma_1^2 \neq \sigma_2^2$.

Then the distribution of $X_2|X_1$ is not a function of the conditional mean alone.

Theorem 1 motivates our approach to infer conditional dependences, or edges in the CIG, via variable selection for many nonlinear regressions, i.e. determining whether a variable X_i is relevant in $\mathbb{E}[X_j|\mathbf{X} \setminus \{X_j\}]$ (regression of X_j versus all other variables).

79 2.2. Ranking Edges

In order to determine which edges should be included in the graphical model, the edges suggested by the individual regressions need to be ranked such that a smaller rank indicates a better candidate for inclusion¹. Note that each edge i - j is associated with two coefficients $(X_j \text{ regressed on } X_i$ and all other variables and vice versa for X_i on X_j). To be conservative, we rank each edge i - j relative to the smaller one of the two (absolute-valued) ranking coefficients.

If variables are mixed-type, a global ranking criterion is difficult to find. 87 For example, **continuous and categorical** response variables are not di-88 rectly comparable. Instead, local rankings for each regression are performed 89 separately (where "local" means that we can rank the importance of predic-90 tors for every individual regression). Analogous to global ranking, each edge 91 i-j is associated with two possible ranks and the worse among them is used. 92 When using Random Forests for performing the individual nonlinear re-93 gressions, the ranking scheme is obtained from Random Forests' variable 94 importance measure. For Conditional Forests, both the conditional 95 and marginal variable importances can be used. When using the 96

⁹⁷ LASSO for individual linear or logistic regressions, the ranking scheme is

¹For instance, if all variables are continuous, the size of the standardized regression coefficients from ordinary least squares is an obvious global ranking criterion. Analogously, in a situation where all variables are binary (and identically coded), coefficients from linear logistic regression lead to a global ranking.

⁹⁸ obtained from the value of the penalty parameter λ for which an es-⁹⁹ timated regression coefficient first becomes non-zero (i.e. the value ¹⁰⁰ of the penalty parameter when a variable enters in a coefficient ¹⁰¹ path plot).

We then have to decide on the number of edges to select, i.e. the tuning parameter. Say it is given as q = 11. Then, for both global and local rankings, we select the 11 best-ranked edges across all p individual regressions. If this is impossible due to tied ranks (e.g. because the 11th and 12th best edges have a tied rank of 11.5), we neglect these (here: two) tied edges and select only the remainder of (here: 10) edges not in violation of the tuning parameter.

We next outline how Stability Selection can be used to guide the choice of q.

110 2.3. Aggregating Edge Ranks with Stability Selection

Stability Selection (Meinshausen and Bühlmann, 2010) allows the specification of an upper bound on the expected number $\mathbb{E}[V]$ of false positives. It is based on subsampling (Politis et al., 1999; Bühlmann and Yu, 2002) random subsets $\mathbf{X}^{(1)}, \ldots, \mathbf{X}^{(n_{sub})}$ of the original sample $\mathbf{X}_1, \ldots, \mathbf{X}_n$, where each $\mathbf{X}^{(k)}$ contains $\lfloor n/2 \rfloor$ sample points.

Let $\mathcal{E}(\hat{G}_{\text{CIG}}(\mathbf{X}^{(k)}))$ denote the edges from a thresholded ranking based on $\mathbf{X}^{(k)}$, $k = 1, \ldots, n_{\text{sub}}$. Stability Selection suggests to construct $\mathcal{E}(\hat{G}_{\text{CIG}}(\mathbf{X}))$, the set of all edges in the estimated CIG of \mathbf{X} , from all edges that were "sufficiently stable" across the n_{sub} subsets. More concretely, we choose only edges i - j which fulfill

$$\frac{1}{n_{\text{sub}}} \sum_{k=1}^{n_{\text{sub}}} I_{\{i-j \in \mathcal{E}(\hat{G}_{\text{CIG}}(\mathbf{X}^{(k)}))\}} \ge \pi_{\text{thr}},\tag{1}$$

where π_{thr} imposes a threshold on the minimum relative frequency of edges across the n_{sub} subsets to be included in $\mathcal{E}(\hat{G}_{\text{CIG}}(\mathbf{X}))$ and I is the indicator function.

In their Theorem 1, Meinshausen and Bühlmann (2010) relate $\mathbb{E}[V]$ to the maximum number of selected edges q per subset, the number of possible edges $p \cdot (p-1)/2$ in $\mathcal{E}(\hat{G}_{\text{CIG}}(\mathbf{X}))$, and the threshold π_{thr} from formula (1) (requiring $\pi_{\text{thr}} \in (\frac{1}{2}, 1)$):

$$\mathbb{E}[V] \le \frac{q^2}{(2\pi_{\rm thr} - 1) \cdot p \cdot (p - 1)/2}.$$
(2)

The expected number of false positives $\mathbb{E}[V]$, which is a type I error 119 measure, needs to be specified a priori. The parameters π_{thr} and q are tuning 120 parameters that depend on each other. More precisely, to obtain a stable 121 graph estimate for a given $\mathbb{E}[V]$, the threshold π_{thr} has to be large if the 122 number of selected edges q is large and vice versa. Consequently (and as also 123 argued by Meinshausen and Bühlmann, 2010) the actual values of π_{thr} and q 124 are of minor importance for a given $\mathbb{E}[V]$ as the graph estimates do not vary 125 much for different choices of π_{thr} (results not shown). We thus fix $\pi_{thr} = 0.75$ 126 throughout the paper. Also, we follow the suggestion of Meinshausen and 127 Bühlmann (2010) in choosing $n_{sub} = 100$. 128

We can then use formula (2) to derive

$$q = \left\lfloor \sqrt{(2\pi_{\rm thr} - 1)\mathbb{E}[V] \cdot p \cdot (p - 1)/2} \right\rfloor$$

¹²⁹ by specifying the value of $\mathbb{E}[V]$ as desired (according to the willingness to ¹³⁰ accept false positives).

Note that formula (2) is based on two assumptions: 1) the estimation 131 procedure is better than random guessing and 2) the probability of a false 132 edge to be selected is exchangeable; for details we refer to Meinshausen and 133 Bühlmann (2010). Also note that π_{thr} is not to be interpreted as an edge 134 probability threshold but solely as a means to assess stability which allows 135 control of $\mathbb{E}[V]$. Finally, be aware that our method does not consider the 136 goodness-of-fit of the model but instead leads to an undirected graph whose 137 edges are controlled for false positive selections. 138

139 3. Random Forests, Conditional Forests, LASSO Regression, and 140 Maximum Likelihood

141 3.1. Random Forests

Random Forests have, to date, not been used to estimate CIGs. They 142 perform a series of recursive binary partitions of the data and construct the 143 predictions from terminal nodes. Based on classification and regression trees 144 (Breiman et al., 1984) they allow convenient inference for mixed-type vari-145 ables, also in the presence of interaction effects. Incorporating bootstrap 146 (Efron, 1979; Breiman, 1996) and random feature selection (Amit and Ge-147 man, 1997), random subsets of both the observations and the predictors are 148 considered. The relevance of each predictor can be assessed with permuta-140 tion importance (Breiman, 2002), a measure of the error difference between 150

a regular Random Forests fit and a Random Forests fit within which one 151 predictor has been permuted at random to purge its relationship with the 152 response. An implementation of Random Forests in R (R Development Core 153 Team, 2011) is available in the randomForest package (Liaw and Wiener, 154 2002). We chose the number of trees and the number of features randomly 155 selected per tree according to the package defaults. Further extensions 156 (which we did not incorporate) allow to explicitly use the ordinal 157 information of a categorical response: see e.g. the R packages party 158 (Hothorn et al., 2006) and rpartOrdinal (Archer, 2010). 159

Since the goodness-of-fit of continuous and categorical responses is based 160 on mean squared errors and majority votes, respectively, the goodness-of-161 fit and importance measures are not directly comparable across mixed-type 162 responses. Thus a local ranking is derived, where each edge i - j is assigned 163 either the rank of the permutation importance of predictor $X_i^{(k)}$ for response $X_j^{(k)}$ or of predictor $X_j^{(k)}$ for response $X_i^{(k)}$ (whichever is more conservative, i.e. assigns a worse rank) and finally aggregated with Stability Selection; the 164 165 166 upper index $^{(k)}$ denotes the k^{th} subsample in Stability Selection. We refer to 167 this procedure as Graphical Random Forests (GRaFo) henceforth. 168

169 3.2. Conditional Forests

Strobl et al. (2007) criticized Random Forests to favor variables with many categories. Furthermore, Random Forests have been criticized to favor correlated predictors, even if not all of them are influential for the response² (Strobl et al., 2008).

To overcome the first limitation, Conditional Forests (Strobl et al., 2007) were suggested, which are a modification of the original Random Forests implementation. They are based on conditional inference trees (Hothorn et al., 2006), an unbiased tree learning procedure, to obtain an unbiased ensemble of trees.

While the regular marginal permutation importance discussed in the previous section is also applicable to Conditional Forests, a conditional permutation importance, which aims to preserve the correlation structure among predictors, has been suggested by Strobl et al. (2008) to overcome the latter critique of forest ensembles fa-

 $^{^{2}}$ This aspect though may be considered as both a source of bias and a beneficial effect as correlated predictors may help to localize relevant structures (Nicodemus et al., 2010)

voring correlated predictors. An implementation of Conditional 184 Forests, including the conditional variable importance, is available 185 in the party package (Hothorn et al., 2006) in R. However, we 186 found that the computational cost to obtain the conditional vari-187 able importance is a lot higher than for the marginal permutation 188 importance. When drastically reducing the number of trees to 10, 189 the computations become feasible but the ensemble does hardly 190 produce any true positives (likely due to instability of the small 191 forest ensemble). As such, all calculations reported further below 192 have been performed using the marginal permutation importance. 193 To allow a fair comparison, we set the ensemble size to 500 trees 194 (as with Random Forests). 195

The same ranking rule as for Random Forests can then be used to construct a Stable Conditional Forest (StabcForests) algorithm.

¹⁹⁸ 3.3. Least Absolute Shrinkage and Selection Operator (LASSO)

In the case of linear regression for continuous responses and predictors, 199 the LASSO (Tibshirani, 1996) penalizes with the ℓ_1 -norm and correspond-200 ing penalty parameter λ the coefficients of some less relevant predictors to 201 zero. The larger λ is chosen, the more coefficients will be set to zero. This 202 concept has also been extended to logistic regression (Lokhorst, 1999) and 203 implemented in R in the glmnet package (Friedman et al., 2010). In the case 204 of multinomial and mixed-type data, no eligible off-the-shelf implementation 205 of the LASSO is available. We hence dichotomize these data according to a 206 median split for continuous variables and aggregate categories such that the 207 resulting frequency of the -1 and 1 categories was as balanced as possible for 208 discrete variables. Consequently, a loss of information is to be expected (cf., 209 MacCallum et al., 2002; Altman and Royston, 2006; Royston et al., 2006). 210

CIG estimation via the LASSO with Stability Selection was suggested for Gaussian data by Meinshausen and Bühlmann (2010) and can be represented as a global ranking. For each response $X_j^{(k)}$, we estimate LASSO regressions with all remaining $\mathbf{X}^{(k)} \setminus \{X_j^{(k)}\}$ as predictors and with a decreasing sequence of penalties $\lambda_j^{(k),\max},\ldots,\lambda_j^{(k),\min}$. Let $\lambda_{ij}^{(k)}$ denote the largest penalty value of the sequence for which the coefficient of predictor $X_i^{(k)}$ for response $X_j^{(k)}$ is non-zero, and if no such penalty exists let $\lambda_{ij}^{(k)} = 0$. For each edge i - j we select the more conservative penalty $\lambda_{i-j}^{(k)} = \min\left(\lambda_{ij}^{(k)}, \lambda_{ji}^{(k)}\right)$ and rank i - j relative to the global rank from the absolute-valued estimated regression coefficient corresponding to $\lambda_{i-j}^{(k)}$. As before, the upper index ^(k) denotes the k^{th} subsample from Stability Selection. We denote this procedure in combination with Stability Selection as Stable LASSO (StabLASSO).

223 3.4. Maximum Likelihood

Ordinary maximum likelihood (ML) estimation does neither impose a penalty (such as the LASSO) nor does it use subsampling to reduce the number of predictors to consider in each run (such as the Forest-type algorithms). Consequently, ordinary ML inference can only be applied in the case, where the number of parameters to be estimated is at most as large as the sample size n.

If the dependent variable is continuous, we use the ordinary linear model, otherwise the multinomial log-linear model. Local rankings are obtained from the F-Test for each of the predictor variables. The calculations were performed with the regr0 package (available from R-Forge) in R.

We could wrap a Stability Selection scheme around ML estimation which is computationally demanding in the case of mixed continuous and categorical variables. Our main goal here, however, is to compare with plain ML estimation.

239 4. Simulation Study

240 4.1. Simulating Data from Directed Acyclic Graphs

We use a directed acyclic graph (DAG; cf., Whittaker, 1990) to embed conditional dependence statements among nodes representing the *p* random variables. The associated CIG follows by moralization, i.e. connecting any two parents with a common child that are not already connected and removing all arrowheads (Lauritzen and Spiegelhalter, 1988).

Let \mathcal{A} be a $(p \times p)$ -dimensional weight matrix with entries $a_{ij} \in \{[-1, -0.1] \cup \{0\} \cup [0.1, 1]\}$ if i < j and $a_{ij} = 0$ otherwise. In addition, we sample \mathcal{A} to be sparse, i.e. we expect only one percent of its entries to deviate from 0. The non-zeros in \mathcal{A} encode the directed edges in a DAG we simulate from similarly as in Kalisch and Bühlmann (2007); see also Table 1. For the Gaussian setting with interaction effects, we furthermore sample $b_{ikj} \in \{[-1, -0.1] \cup \{0\} \cup [0.1, 1]\}$ for all indices i, k, j where main effects between i, j and k, j are present (cf., Table 1). Also, for all $i, j \in \{1, -0.1\}$

 $\{1, \ldots, p\}$ in the multinomial and mixed setting with $a_{ij} \neq 0$ let u_{ij} and v_{ij} be vectors that we use to impose some additional structure on multinomial variables: 1) at least one category of a multinomial predictor X_i should have an effect opposite to the remainder, 2) the (total) effect of the categories of a multinomial predictor X_i should be positive on some categories of a multinomial response X_j and negative on others. For this purpose, we restrict $u_{ij} = (u_{ij}^{(1)}, \ldots, u_{ij}^{(C_i)})$ and $v_{ij} = (v_{ij}^{(1)}, \ldots, v_{ij}^{(C_j)})$:

$$u_{ij}^{(l)} \in \{-1, 1\} \ \forall l = 1, \dots, C_i \ \text{s.t.} \ -C_i < \sum_{l=1}^{C_i} u_{ij}^{(l)} < C_i,$$
$$v_{ij}^{(s)} \in \{-1, 1\} \ \forall s = 1, \dots, C_j \ \text{s.t.} \ -C_j < \sum_{s=1}^{C_j} v_{ij}^{(s)} < C_j.$$

With these definitions, we sample data from different distributions us-246 ing the inverse link function to relate the conditional mean to all previously 247 sampled predictors. Table 1 describes the settings in detail, covering models 248 with purely Gaussian, purely Bernoulli, purely multinomial, and an alternat-249 ing sequence of Gaussian and multinomial variables ("mixed" setting). The 250 Gaussian setting can be further distinguished into a main effects 251 only setting, a main plus interaction effects setting, and a nonlinear 252 effects setting. For the nonlinear setting the signal was amplified 253 by a factor of 5 to obtain comparable results to the other Gaussian 254 settings. The exact specifications are given in Table 1. 255

256 4.2. Simulating Data from the Ising Model

A common approach to model pairwise dependencies between a set of binary variables is the Ising model with probability function

$$p(\mathbf{x},\Theta) = \exp\left(\sum \theta_{ii} x_i + \sum \theta_{ij} x_i x_j - \Gamma(\Theta)\right)$$
(3)

for realizations $\mathbf{x} \in \mathbf{X}$, normalization constant $\Gamma(\Theta)$, and $(p \times p)$ -dimensional symmetric parameter matrix $\Theta = \{\theta_{ij}\}_{i,j \in \{1,...,p\}}$. From the conditional densities of equation (3) if follows that $\theta_{ij} = 0$ ($\theta_{ij} \neq 0$) implies the absence (presence) of edge i - j in the associated CIG. See also Ravikumar et al. (2010).

We sample the diagonal and the upper-triangular matrix of Θ uniformly from $\{-1, 0, 1\}$ such that the average neighborhood size for each node equals 4. The lower-triangular matrix equals its upper counterpart. We use the

| Distribution | Model | Conditional Mean |
|----------------------|--|---|
| Gaussian Gaussian | $egin{aligned} X_j \sim \mathcal{N}(\mu_j, \sigma^2 = 1) \ X_j \sim \mathcal{N}(\mu_j, \sigma^2 = 1), 	ext{ with } I_j \subseteq \{(i,k): a_{ij} \neq 0, a_{kj} \neq 0 \} \end{aligned}$ | $\mu_j = \sum_{i < j} a_{ij} x_i$ $\mu_j = \sum_{i < j} a_{ij} x_i$ |
| +Interactions | s.t. $ I_j \approx \{(i,k) : a_{ij} \neq 0, a_{kj} \neq 0\} /2$ | $+\sum_{(i,k)\in I_i} b_{ikj} x_i x_k$ |
| Gaussian | $X_j \sim \mathcal{N}(\mu_j, \sigma^2 = 1)$, with $L_j \in \{1, \dots, j\}$ s.t. $ L_j \approx j/2$ | $\mu_j = \sum_{i \in L_j} \tilde{5} a_{ij} x_i$ |
| +Nonlinear | and $\bar{L}_j = \{1, \dots, j\} \smallsetminus L_j$ | + $\sum_{i \in \bar{L}_j} 5a_{ij} \log(x_i)$ |
| Bernoulli | $X_j = 2\widetilde{X}_j - 1,$ | $\pi_j = rac{\exp(\sum_{i < j} a_{ij} x_i)}{1 + \exp(\sum_{i < j} a_{ij} x_i)}$ |
| | $\widetilde{X}_{j} \sim \mathcal{B}(1,\pi_{j})$ | |
| Multinomial | $X_j \sim \mathcal{M}(\boldsymbol{\pi}_j = (\pi_j^{(1)}, \dots, \pi_j^{(C_j)})),$ | $\pi_j^{(s)} = \frac{\exp(\eta_j^{(s)})}{\sum_{i,\text{ exp}(n_i^{(r)})}}$ |
| | $\eta_{j}^{(s)} = \sum_{i < j} v_{ij}^{(s)} a_{ij} \sum_{l=1}^{C_i} u_{ij}^{(l)} (2I_{\{x_i=l\}} - 1), \\ C_j \sim \mathcal{U}\{3, 4, 5\}, \ s = 1, \dots, C_j$ | 6. × 1 1=4 - |
| | $\int \mathcal{N}(\mu_i, \sigma^2 = 1), \qquad \text{if } \frac{j}{2} \notin \mathbb{N}$ | $\mu_j = \eta_j^{(1)}$ |
| Mixed | $X_j \sim \left\{ \mathcal{M}(\boldsymbol{\pi}_j = (\pi_j^{(1)}, \dots, \pi_j^{(C_j)})), \text{ else} \right\}$ | $\pi_j^{(s)} = \frac{\exp(\eta_j^{(s)})}{\sum_{i \in \operatorname{exp}(n_i^{(r)})}}$ |
| | $\eta_j^{(s)} = \sum_{i:i < j \land \frac{i}{2} \notin \mathbb{N}} v_{ij}^{(s)} a_{ij} x_{ij} +$ | 61 × 3 1=47 |
| | $+ \sum_{i:i < j \land \frac{1}{2} \in \mathbb{N}} v_{ij}^{(s)} a_{ij} \sum_{l=1}^{C_i} u_{ij}^{(l)} (2I_{\{x_i = l\}} - 1)$ | |
| | $C_j \sim \mathcal{U}\{3,4,	ilde{5}\}, \ s=1,\ldots,C_j$ | |

dependence relationships among the random variables. The scalars $u_{ij}^{(t)}$ and $v_{ij}^{(s)}$ are chosen from $\{-1,1\}$ to impose additional structures on multinomial random variables. I_j is a random set of index numbers, s.t. the number of interactions respectively, where $C_1 \sim \mathcal{U}\{3,4,5\}$. The weights a_{ij} and b_{ikj} are chosen from $\{[-1,-0.1] \cup \{0\} \cup [0.1,1]\}$ to determine the and discrete uniform distribution, respectively. Initial values for X_1 are sampled with $\mu_1 = 0$, $\pi_1 = \frac{1}{2}$, and $\pi_1 = (\frac{1}{C_1}, \dots, \frac{1}{C_1})$, is about half as big as the number of associations with a non-zero coefficient a_{ij} . L_j is a random set of index Table 1: The table shows the six simulation models based on DAGs. $\mathcal{N}, \mathcal{B}, \mathcal{M}, \text{and } \mathcal{U}$ are the Gaussian, Bernoulli, multinomial. numbers, s.t. about half of the associations are linear and the other half are nonlinear. Gibbs sampler (cf., Givens and Hoeting, 2005) to sample realizations from equation (3). Höfling and Tibshirani (2009) provide an implementation in the BMN package in R.

4.3. Simulation Results: Gaussian, Binomial, Multinomial, Mixed, and Ising 268 For $p \in \{50, 100, 200\}$ variables and samples of size n = 100, each of the 269 5 simulation models³ was averaged over 50 repetitions. More precisely, for 270 a given q, the number of observed true and false positives across the 50 271 repetitions was averaged. The results are shown in Figures 1-6. Error control 272 for small bounds on the expected number of false positives $\mathbb{E}[V]$ could be 273 achieved for both GRaFo and StabLASSO in all but the mixed setting with 274 p = 200 in Figure 6. 275

In the Gaussian, Bernoulli and Ising settings, StabLASSO seems to perform slightly better than GRaFo for small error bounds and rather similar across the figures for the true/false positive rates (third column of Figures 1-3). Note that StabLASSO sets many coefficients to 0. As a consequence, a large proportion of edges cannot be selected for false positive rates smaller than 1 resulting in some StabLASSO curves not covering the entire range of the rates.

In the multinomial and mixed setting (Figures 4-6), GRaFo returned 283 satisfactory results while StabLASSO performed poorly, presumably caused 284 by dichotomization. In general, both procedures seem to perform best in the 285 Gaussian setting, followed by the mixed, multinomial, Bernoulli, and Ising 286 setting, respectively. The latter seems especially hard for both procedures if 287 the upper error bound in formula (2) for $\mathbb{E}[V]$ is chosen small. Nevertheless, 288 given one's willingness to expect more errors, the rate figures indicate the 289 potential to recover (parts of) the true structure (cf., Ravikumar et al., 2010; 290 Höfling and Tibshirani, 2009). 291

The "raw" counterparts, Random Forests and LASSO, correspond to estimations and rankings performed on the full data set without Stability Selection. Consequently, these approaches lack any guidance on choosing q. The rate figures were obtained by evaluation of the graphs arising from various values of q. We provide them as a means to check if introducing Stability Selection has any additional (positive or negative) effect on the performance

 $^{^{3}}$ In this section, the Gaussian setting refers to the first model in Table 1, i.e. the Gaussian setting without interaction effects and without nonlinear effects.

of the Random Forests and LASSO methods besides enabling us to choose q. From the rate figures, we can deduce that the raw methods perform quite similar to GRaFo and StabLASSO across all settings. Hence, the use of Stability Selection did not introduce any surprising new behavior of Random Forests or LASSO.

A violation of condition (A) of Theorem 1 in the mixed setting could 303 explain the failure of both GRaFo and StabLASSO to achieve error control 304 for p = 200. However, both the mixed setting with p = 50 and p = 100 returned 305 very few observed errors and remained well below the error bounds indicating 306 the problematic behavior may be linked to larger values of p. Also, for any 307 setting it is unlikely that the exchangeability assumption holds. Meinshausen 308 and Bühlmann (2010) argue that Stability Selection appears to be robust to 309 violations, but did not study mixed data which may be particularly affected. 310 We study this aspect more closely further below. 311

The computational cost is growing rather quickly with growing p. The 312 runtime of a single of the 50 repetitions per setting is in the order of 15 313 minutes for GRaFo and 20 minutes for StabLASSO for p = 50 and increases 314 to several hours for GRaFo and 30 minutes for StabLASSO in the case of 315 p = 200. Each batch of 50 repetitions was run in parallel on 50 cores of 316 the BRUTUS high-performance cluster comprising quad-core AMD Opteron 317 8380 2.5 Ghz CPUs with 1 GB of RAM per core using the Rmpi package 318 (Yu, 2010) available in R. 319

320 4.4. Simulation Results: Gaussian with Interaction Effects

For $p \in \{50, 100, 200\}$ variables and samples of size n = 100, each 321 graph in Figure 7 was averaged over 50 repetitions. The results 322 appear very similar to our findings for the Gaussian model with-323 out interactions and without nonlinear effects. However, here the 324 number of true positives is somewhat lower for both GRaFo and 325 StabLASSO with an (arguably) slightly smaller drop for the GRaFo 326 procedure. This does not seem too surprising, given that Ran-327 dom Forests have the ability to incorporate interactions naturally, 328 whereas they have to be specified explicitly for the LASSO (which 320 has not been done here). 330

However, overall the total number of interaction terms is relatively small, ranging from roughly 5% to 10% of all model terms. For a larger number of interaction terms, we would thus expect a further gain of the GRaFo over the StabLASSO procedure.



Figure 1: The rows correspond to the Gaussian, Bernoulli, and Ising model with p = 50. Their true CIGs have 16, 16 and 89 edges, respectively. The first two columns report the observed number of true and false positives ("o") relative to the bound in (2) for the expected number $\mathbb{E}[V]$ of false positives ("]") for GRaFo and StabLASSO, respectively, averaged over 50 simulations. The third column reports the averaged true and false positive rates of GRaFo and StabLASSO relative to the performance of their "raw" counterparts without Stability Selection.



Figure 2: The rows correspond to the Gaussian, Bernoulli, and Ising model with p = 100. Their true CIGs have 58, 58 and 182 edges, respectively. The first two columns report the observed number of true and false positives ("o") relative to the bound in (2) for the expected number $\mathbb{E}[V]$ of false positives ("]") for GRaFo and StabLASSO, respectively, averaged over 50 simulations. The third column reports the averaged true and false positive rates of GRaFo and StabLASSO relative to the performance of their "raw" counterparts without Stability Selection.



Figure 3: The rows correspond to the Gaussian, Bernoulli, and Ising model with p = 200. Their true CIGs have 334, 334 and 369 edges, respectively. The first two columns report the observed number of true and false positives ("o") relative to the bound in (2) for the expected number $\mathbb{E}[V]$ of false positives ("]") for GRaFo and StabLASSO, respectively, averaged over 50 simulations. The third column reports the averaged true and false positive rates of GRaFo and StabLASSO relative to the performance of their "raw" counterparts without Stability Selection.



Multinomial and mixed-type models, p = 50

Figure 4: The rows correspond to the multinomial and mixed-type model with p = 50. Their true CIGs both have 16 edges. The first two columns report the observed number of true and false positives ("o") relative to the bound in (2) for the expected number $\mathbb{E}[V]$ of false positives ("]") for GRaFo and StabLASSO, respectively, averaged over 50 simulations. The third column reports the averaged true and false positive rates of GRaFo and StabLASSO relative to the performance of their "raw" counterparts without Stability Selection.



Multinomial and mixed-type models, p = 100

Figure 5: The rows correspond to the multinomial and mixed-type model with p = 100. Their true CIGs both have 58 edges. The first two columns report the observed number of true and false positives ("o") relative to the bound in (2) for the expected number $\mathbb{E}[V]$ of false positives ("]") for GRaFo and StabLASSO, respectively, averaged over 50 simulations. The third column reports the averaged true and false positive rates of GRaFo and StabLASSO relative to the performance of their "raw" counterparts without Stability Selection.



Multinomial and mixed-type models, p = 200

Figure 6: The rows correspond to the multinomial and mixed-type model with p = 200. Their true CIGs both have 334 edges. The first two columns report the observed number of true and false positives ("o") relative to the bound in (2) for the expected number $\mathbb{E}[V]$ of false positives ("]") for GRaFo and StabLASSO, respectively, averaged over 50 simulations. The third column reports the averaged true and false positive rates of GRaFo and StabLASSO relative to the performance of their "raw" counterparts without Stability Selection.



Figure 7: Gaussian model with interactions with p = 50, 100, and 200. Their true CIGs have 16, 58, and 334 edges, respectively, with 1, 6, and 21 first-order interaction terms. The first two columns report the observed number of true and false positives ("o") relative to the bound in (2) for the expected number $\mathbb{E}[V]$ of false positives ("]"), respectively, averaged over 50 simulations. The third column reports the averaged true and false positive rates of GRaFo and StabLASSO relative to the performance of their "raw" counterparts without Stability Selection.

335 4.5. Simulation Results: Gaussian with Nonlinear Effects

For $p \in \{50, 100, 200\}$ variables and samples of size n = 100, each 336 graph in Figure 8 was averaged over 50 repetitions. Here, GRaFo 337 clearly outperforms StabLASSO in terms of true positives for all 338 considered p. However, for GRaFo the number of false positives is 339 not controlled by a small bound on $\mathbb{E}[V]$ anymore for p > 50, which is 340 especially apparent in the case where p = 200. For StabLASSO there 341 seems to be a similar behavior, but only for p = 200 the number of 342 false positives clearly violates $\mathbb{E}[V]$. The "raw" Random Forests 343 and LASSO estimates show very similar results to their Stability 344 Selection counterparts. Note that the signal has been amplified by 345 a factor of 5 to achieve comparable performance of the estimation 346 procedures to the linear Gaussian setting. 347

348 4.6. Simulation Results: Mixed-Setting with ML and StabCForests

The first row of Figure 9 reports for p = 50 and n = 500 the re-349 sults of ML estimation, GRaFo, and StabLASSO, averaged over 50 350 runs. Not surprising, both GRaFo and StabLASSO perform better 351 than in the setting where n = 100, though StabLASSO remains at 352 a clear disadvantage due to the unfavorable dichotomization. On 353 the other hand, the performance of GRaFo (and also its "raw" 354 Random Forests counterpart) is on par with the ML estimation. 355 Stability Selection was not applied to ML estimation due to the im-356 mense computational burden and thus no bounds on $\mathbb{E}[V]$ could be 357 specified. However, for both GRaFo and StabLASSO we find that 358 the number of false positives are typically well below the specified 359 bounds. 360

The second and third row of Figure 9 report the performance of 361 StabcForests and GRaFo for p = 50 and p = 100 with n = 100, averaged 362 over 50 runs. The GRaFo results from above are reproduced for 363 better readability. We find that both GRaFo and StabcForests 364 show very similar results. In the first two columns we see that 365 GRaFo seems to perform somewhat better for very small bounds 366 on $\mathbb{E}[V]$. The performance of the two "raw" methods is very similar 367 to their stable counterparts. 368

The computational burden of StabcForests is much larger than for GRaFo and amounts to roughly 2 hours for p = 50 and roughly for 0 hours for p = 100. Also note that the reported results within



Figure 8: The rows correspond to the Gaussian with nonlinear associations with p = 50, 100, and 200. Their true CIGs have 16, 58, and 334 edges, respectively. The first two columns report the observed number of true and false positives ("o") relative to the bound in (2) for the expected number $\mathbb{E}[V]$ of false positives ("]") for GRaFo and StabLASSO, respectively, averaged over 50 simulations. The third column reports the averaged true and false positive rates of GRaFo and StabLASSO relative to the performance of their "raw" counterparts without Stability Selection.

the Conditional Forests framework use the marginal permutation importance due to the very heavy computational burden of the conditional variable importance.

375 5. Functional Health in the Swiss General Population

376 5.1. The Importance of Functional Health

According to the World Health Organization's (WHO) new framework of 377 the International Classification of Functioning, Disability and Health (ICF; 378 cf., WHO, 2001) the lived experience of health (Stucki et al., 2008) can 379 be structured in experiences related to body functions and structures as 380 well as to activity and participation in society. All of these are, in turn, 381 influenced by a variety of so-called personal factors such as gender, income, 382 or age and environmental factors including individual social relations and 383 supports as well as properties of larger macro social systems such as the 384 economy (see Figure 10). Also, the WHO and The World Bank recommend 385 in their recent World Report on Disability (2011) that functional health 386 state descriptors are analyzed in conjunction with other health outcomes and, 387 particularly, that more research is conducted on "[...] the interactions among 388 environmental factors, health conditions, and disability [...]" (p. 267 WHO 380 and The World Bank, 2011). Under these prerequisites it is of interest which 390 variables are conditionally dependent on each other. For instance, "Does the 391 income distribution affect participation, conditional on known impairments, 392 environmental, and personal factors?". 393

394 5.2. Study Population

We use GRaFo for a secondary analysis of cross-sectional observational 395 data on functional health from the Swiss Health Survey (SHS) in 2007. Data 396 were obtained from the Federal Statistics Office of Switzerland. The original 397 study was based on a stratified random sample of all private Swiss households 398 with fixed line telephones. Within each household one household member 390 aged 15 or older was randomly selected. The survey was completed by a 400 total of 18760 persons, corresponding to a participation rate of 66 percent 401 (Graf, 2010). The mean age of study participants was 49.6 years (± 18.5). 402 The data were mostly collected with computer assisted telephone interviews. 403 Further information is available elsewhere (Storni, 2011). 404



Figure 9: The rows correspond to applications of ML and StabcForests to data from the mixed model with varying p and n. For p = 50 (p = 100), the true CIG has 16 (58) edges. The first two columns report the observed number of true and false positives ("o") relative to the bound in (2) for the expected number $\mathbb{E}[V]$ of false positives ("]") for GRaFo and StabLASSO or StabcForests, respectively, averaged over 50 simulations. The third column reports the averaged true and false positive meters.



Figure 10: The International Classification of Functioning, Disability and Health (ICF) model relates aspects of human functioning and provides a common language for practitioners.

405 5.3. Variables

The SHS included various information on symptoms (in particular pain), 406 impairments, and activity limitations. Since the respective items were some-407 times nominal, sometimes ordinal, and sometimes (e.g. body mass index) 408 metric, we dichotomized each item so that 1 was indicative of having any 409 kind of problem. As overall summary scores on functioning and disability 410 were not recommendable (Reinhardt et al., 2010), we followed the framework 411 of the WHO's biopsychosocial model of health, outlined in the ICF (WHO, 412 2001, see Figure 10), and other theoretical considerations (WHO and The 413 World Bank, 2011; Reinhardt et al., 2010) in constructing sum indices (see 414 Table 2). The plausibility of all indices was checked using the Stata 11 con-415 firmatory factor analysis module confa (Kolenikov, 2009). In each case the 416 index construction was tested and the null hypothesis of a diagonal structure 417 of the covariance matrix rejected. 418

We created a dummy variable for labor market participation restrictions 419 such that 1 identified persons who gave up work, reduced the number of 420 working hours, or changed jobs because of health reasons. We also created a 421 dummy variable for participation in leisure physical activity (LPA) differen-422 tiating between people participating in leisure activities leading to sweating 423 at least once a week and those who do not. General health perception was 424 measured with the following question and answer options: "How would you 425 rate your health in general? Very good, good, fair, poor, or very poor?". 426 We further included indicators of socio-economic status (SES) in our anal-427 ysis: equivalence household income, years of formal education, employment 428 status, and migration background (foreign origin of at least one parent). On 429 the macro- or cantonal-level we obtained information on the Swiss counties' 430 (cantons) gross domestic products (GDP), Gini coefficients, and crime rates 431 for 2006. Moreover, we considered information on gender, age, marital sta-432 tus (being married), alcohol consumption (in grams per day), and current 433 smoking (yes/no). 434

Of these, in total, 20 mixed-type variables (see Table 3), income had the highest number of missing values with roughly 6 percent. Overall, less than 0.85 percent of replies were missing corresponding to 2687 cases with one or more missing values. To assess their effect, we estimated the CIG once with casewise deletion and once with imputation of missing values with the missForest procedure (Stekhoven and Bühlmann, 2011) available in R. An alternative would be to use surrogate splits, which may be particularly



Figure 11: Conditional independence graph of the p = 20 variables (nodes) remaining after construction of indices based on the 2007 Swiss Health Survey estimated with GRaFo. Edges were selected with respect to an upper bound of 5 on the expected number of false positives, see formula (2). Five nodes (social network utilization, migration background, smoker, work restriction, and LPA) were isolated (no edges) and thus neglected.

feasible if the speed of the imputation method is of importance (Hapfelmeier et al., 2012).

444 5.4. Research Hypothesis

From the WHO's ICF model (WHO, 2001, see Figure 10), we hypothesized that all variables on functional and general health perception, and all variables on social status, networks, and supports were connected via paths within the same component of the CIG.

449 5.5. *Findings*

Figure 11 shows the resulting graph from our application of GRaFo to the (non-imputed) data on functional health from the SHS with casewise deletion of missing values regularized for a bound (as in formula (2)) for an expected number of false positives $\mathbb{E}[V] \leq 5$. The selected edge sets for the imputed and casewise deleted data were quite similar for various bounds on $\mathbb{E}[V]$ and even identical for $\mathbb{E}[V] \leq 5$ (not shown). In the following, we thus focus

| Construct | Variable specification |
|---|--|
| Impairment | Problems with vision hearing speaking body mass index (i.e. over 30 or under 16) urinary incontinence defecation feeling weak, tired, or a lack of energy sleeping tachycardia |
| Pain | Range of sum index: 0-9 Pain in head chest stomach back hands joints |
| Activity & participation limitation | Range of sum index: 0-6 Problems with independently walking eating getting up from bed or chair dressing using the toilet taking a shower or bath preparing meals using a telephone doing the laundry caring for finances/accounting using public transport doing major household tasks doing shopping |
| Social support | Range of sum index: 0-13 Having no feelings of loneliness no desire to turn to someone at least one supportive family member someone to turn to |
| Social network utilization | Range of sum index: 0-4 At least weekly visits from family phone calls with family visits from friends phone calls with friends participation in clubs/associations/parties Range of sum index: 0-5 |

Table 2: Construction rules of sum indices for functioning (pain, impairment, activity and participation limitation) and social integration (social support and social network utilization) from 37 dichotomous (yes=1/no=0) variables.

| Туре | Variable | % Missing |
|----------------|--|-----------|
| > 2 categories | Impairment index | 5.92 |
| | Pain index | 0.37 |
| | Activity limitation index | 0.69 |
| | Social support index | 5.84 |
| | Social network utilization index | 2.32 |
| | General health perception | 0.05 |
| Dichotomous | Male | 0.00 |
| | Married | 0.09 |
| | Paid work | 0.03 |
| | Migration background | 4.73 |
| | Smoker | 0.07 |
| | Work restriction | 0.00 |
| | Leisure physical activity | 0.00 |
| Continuous | Age | 0.00 |
| | Years of formal education | 0.07 |
| | Income | 5.94 |
| | Alcohol consumption (in grams per day) | 2.59 |
| | Gross domestic product | 0.00 |
| | Gini coefficient | 0.00 |
| | Crime rate | 0.00 |

Table 3: List of all 20 variables used in the CIG estimation, their type, and their percentage of missing values.

on the CIG derived from the complete observations remaining after casewise
deletion of missing values. As the data contains mixed-type variables we
did not perform a similar analysis with the LASSO (clearly non-favorable
dichotomization was used in the simulations in Section 4.3).

The resulting edges for $\mathbb{E}[V] \leq 1$ depict relatively obvious associations 460 known from everyday observations. Interestingly, general health perception 461 is conditionally dependent on activity limitation but conditionally indepen-462 dent of impairment and pain. In the larger graph for $\mathbb{E}[V] \leq 5$, one sees that 463 general health perception, impairments, and pain are connected through a 464 path of several environmental and personal factors such as social support, 465 being married, age, etc. That implies, for instance, that we do not need 466 information on impairment to predict general health perception if we have 467 information on activity limitation and the remaining predictors, whereas ac-468 tivity limitation is an essential predictor of general health perception even if 460 information on all the remaining predictors is provided. For instance, a per-470 son with a spinal cord injury who has no activity limitation because of social 471 and technological supports, could thus still report good health. This finding 472 is supported by other sources reporting that many people with disabilities 473 do not consider themselves to be unhealthy (WHO and The World Bank, 474 2011; Watson, 2002). In the 2007-2008 Australian National Health Survey. 475 40 percent of people with a severe or profound impairment rated their health 476 as good, very good, or excellent (Australian Bureau of Statistics, 2009). 477

As regards our hypothesis derived from the ICF model (WHO, 2001). 478 we can confirm that the bulk of individual level variables form one com-479 ponent and support the biopsychosocial model of health: Functional and 480 general health influence each other and are connected with a variety of en-481 vironmental and personal factors. However, not all candidate personal and 482 environmental factors were related in our study. This may be due to our 483 conservative upper bound on the error that is likely to favor false negatives, 484 i.e. missing edges. There may also be an issue with our selection of variables 485 that was restricted by the choices of the original survey team. In particular, 486 macro-level variables pertaining information about the counties, in which the 487 individuals are nested, form a second component. It may be that their effect 488 is already contained in the individual-level variables, for example paid work. 489 Five variables do not appear in the graph entirely: social network utilization, 490 migration background, smoker, work restriction, and LPA. If we remove the 491 three macro-level variables GDP, Gini, and crime rate from the model, the 492 connectivity of the individual-level component does not change. Instead, the 493

two variables migration background and social network utilization are now present as a separate component (not shown).

Unfortunately, lack of information on the directions of relationships is a 496 weakness of CIGs. Also, condition (A) of Theorem 1 and the exchangeability 497 condition have likely been violated. One disadvantage of the randomForest 498 implementation is the inability to model continuous variables with < 6 unique 499 values, which may oftentimes be an issue for the sum indices in combination 500 with subsampling. Consequently, we chose to model them as categorical 501 variables. Regardless, given the high face validity of the findings and the 502 achievement of error control in the mixed setting for small p in Section 4.3, 503 the results seem satisfactory. 504

The runtime of GRaFo depends also on n, even if p is small. Hence, estimation of the SHS graph was executed in parallel on 10 cores of the BRUTUS cluster with a runtime of roughly 8 hours.

6. Modeling Neurodevelopment in Children Experiencing Open Heart Surgery

Here we demonstrate an application of GRaFo to a research question, where p is much larger than n. It is thus of particular interest, whether GRaFo can suggest meaningful associations or tends to produce seemingly spurious associations.

514 6.1. Neurodevelopment after Open-Heart Surgery

In children with complex congenital heart disease (CHD) neurological and 515 developmental alterations are common (Bellinger et al., 2003; Snookes et al., 516 2010; Ballweg et al., 2007). The observed cognitive, behavioral, and motor 517 deficits can significantly impact daily routine and educational perspectives 518 and lead to a high rate of special schooling and supportive therapies in this 519 population (von Rhein et al.: Hövels-Gürich et al., 2006, 2008). In severe 520 congenital heart disease requiring open-heart surgery, factors can be further 521 subdivided into pre-, peri-, and post-operative factors. One of the major 522 limitations of studies on patient specific risk-factors (Ballweg et al., 2007; 523 Hövels-Gürich et al., 2006, 2008), treatment and bypass protocols (Bellinger 524 et al., 2003; Snookes et al., 2010), and post-operative complications (Bellinger 525 et al., 2003; Snookes et al., 2010) is the inability to provide a full picture of the 526 interplay of all potentially relevant risk-factors available in the data. Thus, 527 understanding their common association structure is of large interest. 528

529 6.2. Study Population

A group of 221 infants with a congenital heart disease that underwent open-heart surgery with full-flow cardiopulmonary bypass prior to their first birthday from a study of the Children Hospital Zurich from 2004 to 2008 (von Rhein et al.). We restricted our sample to a more homogeneous subpopulation of 34 infants suffering from trisomy 21 of whom 14 were male and 31 caucasian.

536 6.3. Variables

In total, 133 variables were available for modeling. They can further be subdivided into 40 variables describing basic characteristics (e.g. birth parameters, family information), 10 variables characterizing a child's neurodevelopment prior to surgery, 69 peri-operative factors (i.e. data on preoperative, intra-operative, and post-operative course), 13 variables characterizing a child's neurodevelopment 1 year post surgery, and 1 variable summarizing quality of life based on the TAPQOL questionnaire (TNO, 2004).

To ease interpretation, we focus in Table 4 on the 29 variables which had at least one adjacent node in the resulting graph which we discuss below. These variables are of mixed-type, with 23 continuous variables and 6 factors with more than 2 levels.

⁵⁴⁸ Outcome-variables of primary interest are the Bayley score for motor ⁵⁴⁹ development and the Bayley score for cognitive development (Bayley, 1993). ⁵⁵⁰ Both scores were assessed at one year of age.

In total, 3.4 percent of the data were missing, ranging from 87 completely observed variables to 3 variables with 11 missing observations (two Apgar score variables (see also Apgar, 1953) and the child's head circumference at birth (not in graph)). Case-wise exclusion of children with missing values seems infeasible as this would result in the loss of 26 children. Data were thus imputed using the missForest procedure (Stekhoven and Bühlmann, 2011).

557 6.4. Objective

To identify risk-factors associated with the cognitive and motor development of infants that have undergone open-heart surgery in the first 12 months after birth due to a congenital heart disease using GRaFo.

⁵⁶¹ Due to the large number of variables, many methods of analysis ⁵⁶² (such as bivariate correlations) may be prone to yield various spu-⁵⁶³ rious associations. It is here thus also of interest to demonstrate ⁵⁶⁴ that, whenever GRaFo suggests an association, it tends to have

| Scale | Group | Variable | Missing |
|-----------------------|---------------------|---|---------|
| cont | birth/family | Apgar score 5 mins | 11 |
| cont | birth/family | Apgar score 1 mins | 11 |
| cont | birth/family | Apgar score 10 mins | 10 |
| cont | birth/family | birth weight | 1 |
| cont | birth/family | gestational age | 0 |
| cont | birth/family | birth length | 1 |
| cont | birth/family | father age | 1 |
| cont | birth/family | mother age | 0 |
| > 2 | birth/family | father school education | 2 |
| > 2 | birth/family | father professional education | 2 |
| cont | birth/family | socio economic status | 1 |
| > 2 | birth/family | mother school education | 1 |
| > 2 | birth/family | mother number pregnancies | 1 |
| > 2 | birth/family | mother number births gestational age > 24 weeks | 1 |
| cont | peri-operative | time aorta occlusion | 0 |
| > 2 | peri-operative | operation risk | 0 |
| cont | peri-operative | lactate max during surgery | 1 |
| cont | peri-operative | lactate max 24h post surgery | 0 |
| cont | peri-operative | age at surgery | 0 |
| cont | peri-operative | lowest SO2 during surgery | 0 |
| cont | peri-operative | lowest SO2 24h post surgery | 0 |
| cont | peri-operative | length at surgery | 0 |
| cont | peri-operative | weight at surgery | 0 |
| cont | peri-operative | head circumference at surgery | 0 |
| cont | 1 year post surgery | weight at 1 year | 5 |
| cont | 1 year post surgery | length at 1 year | 5 |
| cont | 1 year post surgery | head circumference at 1 year | 5 |
| cont | 1 year post surgery | Bayley motor score | 5 |
| cont | 1 year post surgery | Bayley cognitive score | 6 |

Table 4: List of all 29 variables which appear in the graph, their scale type (> 2 for categorical; cont. for continuous), variable group, and their percentage of missing values.

a high face validity (which is judged by the collaborating healthprofessionals).

567 6.5. Findings

For an upper bound of 5 on the expected number of false positives $\mathbb{E}[V]$ 568 we find that the Balyey scores for motor and cognitive development are only 569 associated with each other, but not with any other node in the graph (con-570 ditional the remainder) in Figure 12. We do, however, find 10 small clusters 571 of high face-validity. For example, the age of each child's father and mother 572 form a common cluster. Likewise, the children's Apgar score after 1 minute 573 is connected with the Apgar score after 5 minutes. The latter furthermore 574 connects with the Apgar score after 10 minutes. It thus seems that GRaFo 575 manages to identify many edges which appear intuitively correct, but it fails 576 to provide new insights into the association structure of the Bayley scores. 577 On the other hand, no apparent "odd" associatons were suggested. 578 This result mirrors current knowledge about the neurodevelopment of in-579 fants after open heart surgery: genetic defects (Bellinger et al., 2003; Snookes 580 et al., 2010; Ballweg et al., 2007) and ethnicity (Ballweg et al., 2007) have 581 been described as relevant risk-factors for adverse neurodevelopment. As we 582 mostly worked with caucasian children, all of whom have trisomy 21, these 583 factors have already been controlled for by the design. Even if we increase 584 the upper bound on $\mathbb{E}[V]$ to 50 we still cannot find any additional variables 585 connected to the Bayley scores. The plausibility of the other observed clus-586

ters would thus suggest, that no stable associations with the Bayley scores can be identified using GRaFo.

However, potential bias induced by the imputation method which also utilizes Random Forests cannot be excluded. For example, all Apgar scores showed a large number of missing values. The identified cluster may thus also be an artifact of the missing value imputation. Furthermore, our choice of variables was determined by the original study design. Also, we cannot guarantee that the exchangeability assumption (Meinshausen and Bühlmann, 2010) and assumption (A) from Theorem 1 hold.

The small number of children $(n \ll p)$ allowed to run this analysis on an AMD Athlon 64 X2 5600+ PC with 6 GB of memory in just under 14 minutes.



Figure 12: The figure shows the conditional independence graph of children with trisomy 21 experiencing open-heart surgery. The reported p = 29 variables (nodes) have at least one adjacent node for an upper bound of 5 on the expected number of false positives $\mathbb{E}[V]$.

599 7. Conclusion

We propose GRaFo (Graphical Random Forests) performed satisfactory, 600 mostly on par or superior to StabLASSO, StabcForests, LASSO, Condi-601 tional Forests, Random Forests, and ML estimation. Error control of 602 false positive edges could be achieved in all but the mixed-type simulation 603 with p = 200 and the nonlinear Gaussian setting with $p \ge 100$. Viola-604 tion of assumption (A) in Theorem 1 and of the exchangeability condition 605 might be responsible for this behavior. In contrast, in most of the other 606 settings GRaFo was very conservative and observed false positive edges were 607 well below their expected upper bound. The Ising model, the sole model 608 not based on DAGs, was particularly hard for both GRaFo and StabLASSO 609 resulting in few true positives if error bounds were chosen very small. 610

Results in the Gaussian setting with interactions were very similar to the main effects Gaussian setting, which is likely due to the small number of interactions in our simulation model. On the contrary, GRaFo shows a clear gain over StabLASSO in the nonlinear setting, where half of the associations were nonlinear in nature.

Poor results for the LASSO in the multinomial and mixed case, where we need dichotomization, may be improved by feasible modifications of the LASSO, such as an extension of the group LASSO (Meier et al., 2008) to multinomial responses (Dahinden et al., 2010). However, penalization if both discrete and continuous variables are included is not a straightforward task (including the issue of scaling).

The ML results indicate that both GRaFo and StabcForests perform very well in the mixed setting, though the computational cost of StabcForests notably exceeds the cost of GRaFo. Both Forests-based algorithms used marginal permutation importance as the conditional permutation importance turned out impractical due to its high computational cost.

The Swiss Health Survey graph consists of an individual- and a macrolevel variable cluster which were highly stable with respect to the way of handling missing values. Exclusion of the macro-level cluster did not affect the individual-level cluster. For a small error bound, our hypothesis that all factors should connect could not be fully confirmed, though a strong tendency toward the ICF's biopsychosocial model of health was evident in the individual-level cluster.

⁶³⁵ The children hospital graph consists of many clusters of high face-validity.

We believe this emphasizes GRaFo's potential to isolate true and 636 stable associations. However, we failed to identify any new potential risk 637 factors that may help to explain adverse neurodevelopment (since no edges 638 connect to the corresponding outcome measures). The known risk factors 639 ethnicity and genetic defects were controlled for by the design. This may 640 be a consequence of the available pool of variables. Also, it is 641 imaginable, that some associations are only of importance for a 642 sub-group of the study. In this case, they would appear to be 643 instable to GRaFo and consequently not be reported. 644

⁶⁴⁵ 8. Proof of Theorem 1

Proof: We know that $X_j \perp X_i | \mathbf{X} \setminus \{X_j, X_i\}$ is equivalent to

$$\mathbb{P}[X_j \le x_j | \{x_h; h \ne j\}] = \mathbb{P}[X_j \le x_j | \{x_h; h \ne j, i\}]$$

$$\tag{4}$$

for all realizations x_j of X_j and $\{x_h; h \neq j\}$ of $\mathbf{X} \setminus \{X_j\}$. Due to assumption (A) we can rewrite (4):

$$F_j(x_j|m_j(\{x_h; h \neq j\})) = F_j(x_j|m_j(\{x_h; h \neq j, i\}))$$
(5)

for all x_j and all $\{x_h; h \neq j\}$. But (5) is equivalent to

$$m_j(\{x_h; h \neq j\}) = m_j(\{x_h; h \neq j, i\})$$
(6)

for all $\{x_h; h \neq j\}$. This completes the proof. 647

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652 10. References

653 References

Altman, D.G., Royston, P., 2006. The cost of dichotomising continuous
 variables. Brit Med J 332, 1080.

- Amit, Y., Geman, D., 1997. Shape quantization and recognition with ran domized trees. Neural Comput 9, 1545–1588.
- Apgar, V., 1953. A proposal for a new method of evaluation of the newborn
 infant . in: 32 (1953),. Curr. Res. Anesth. Analg. 32, 260–267.
- Archer, K.J., 2010. rpartOrdinal: An R package for deriving a classification
 tree for predicting an ordinal response. J Stat Softw 34, 1–17.
- Australian Bureau of Statistics, 2009. National Health Survey: Summary of
 Results, 2007-2008. Australian Bureau of Statistics, Canberra.
- Ballweg, J.A., Wernovsky, G., Gaynor, J.W., 2007. Neurodevelopmental
 outcomes following congenital heart surgery. Pediatr Cardiol 28, 126–33.
- Bayley, N., 1993. Manual for the Bayley Scales of Infant Development. The
 Psychological Corporation, San Antonio, TX.
- Bellinger, D.C., Wypij, D., duPlessis, A.J., Rappaport, L.A., Jonas, R.A.,
 Wernovsky, G., Newburger, J.W., 2003. Neurodevelopmental status at
 eight years in children with dextro-transposition of the great arteries: the
 Boston Circulatory Arrest Trial. J Thorac Cardiov Sur 126, 1385–96.
- ⁶⁷² Breiman, L., 1996. Bagging predictors. Mach Learn 24, 123–140.
- ⁶⁷³ Breiman, L., 2001. Random Forests. Mach Learn 45, 5–32.
- Breiman, L., 2002. Setting Up, Using, And Understanding Random Forests
 V4.0.
- Breiman, L., Friedman, J., Olshen, R., Stone, C., 1984. Classification and
 Regression Trees. Wadsworth, Inc., California.
- ⁶⁷⁸ Bühlmann, P., Yu, B., 2002. Analyzing bagging. Ann Stat 30, 927–961.
- Dahinden, C., Kalisch, M., Bühlmann, P., 2010. Decomposition and model
 selection for large contingency tables. Biometrical J 7, 247–248.
- Efron, B., 1979. Bootstrap methods: Another look at the jackknife. Ann Stat 7, 1–26.
- Friedman, J., Hastie, T., Tibshirani, R., 2008. Sparse inverse covariance
 estimation with the graphical Lasso. Biostatistics 9, 432–441.

- Friedman, J., Hastie, T., Tibshirani, R., 2010. Regularization paths for
 generalized linear models via coordinate descent. J Stat Softw 33, 1–22.
- Givens, G.H., Hoeting, J.A., 2005. Computational Statistics. Hohn Wiley &
 Sons, Inc., New Jersey.
- Graf, E., 2010. Rapport de méthodes. Enquête suisse sur la santé 2007. Plan
 d'échantillonnage, pondérations et analyses pondérées des données. Office
 Fédéral de la Statistique, Neuchâtel.
- Hapfelmeier, A., Hothorn, T., Ulm, K., 2012. Recursive partitioning on incomplete data using surrogate decisions and multiple imputation. Comput
 Stat Data An 56, 1552–1565.
- Höfling, H., Tibshirani, R., 2009. Estimation of sparse binary pairwise
 markov networks using pseudo-likelihoods. J Mach Learn Res 10, 883–
 906.
- Hothorn, T., Hornik, K., Zeileis, A., 2006. Unbiased recursive partitioning: A
 conditional inference framework. Journal of Computational and Graphical
 Statistics 15, 651–674.
- Hövels-Gürich, H.H., Bauer, S.B., Schnitker, R., Willmes-von Hinckeldey,
 K., Messmer, B.J., Seghaye, M.C., Huber, W., 2008. Long-term outcome of speech and language in children after corrective surgery for cyanotic or acyanotic cardiac defects in infancy. Eur J Paediatr Neuro 12, 378–86.
- Hövels-Gürich, H.H., Konrad, K., Skorzenski, D., Nacken, C., Minkenberg,
 R., Messmer, B.J., Seghaye, M.C., 2006. Long-term neurodevelopmental outcome and exercise capacity after corrective surgery for tetralogy of
 Fallot or ventricular septal defect in infancy. Ann Thorac Surg 81, 958–66.
- Kalisch, M., Bühlmann, P., 2007. Estimating high-dimensional directed acyclic graphs with the PC-algorithm. J Mach Learn Res 8, 613–636.
- Kalisch, M., Fellinghauer, B., Grill, E., Maathuis, M.H., Mansmann, U.,
 Bühlmann, P., Stucki, G., 2010. Understanding human functioning using
 graphical models. BMC Med Res Methodol 10, 14.
- Kolenikov, S., 2009. Confirmatory factor analysis using confa. Stata J 9,
 329–373.

- ⁷¹⁶ Lauritzen, S.L., 1996. Graphical Models. Oxford University Press, Oxford.
- Lauritzen, S.L., Spiegelhalter, D.J., 1988. Local computations with probabilities on graphical structures and their application to expert systems (with discussion). J Roy Stat Soc B 50, 157–224.
- Lauritzen, S.L., Wermuth, N., 1989. Graphical models for associations between variables, some of which are qualitative and some quantitative. Ann
 Stat 17, 31–57.
- Liaw, A., Wiener, M., 2002. Classification and regression by randomForest.
 R News 2, 18–22.
- Lokhorst, J., 1999. The Lasso and generalised linear models. Honors project.
 The University of Adelaide, Australia.
- MacCallum, R.C., Zhang, S., Preacher, K.J., Rucker, D.D., 2002. On the
 practice of dichotomization of quantitative variables. Psychol Methods 7,
 19–40.
- Meier, L., van de Geer, S., Bühlmann, P., 2008. The group Lasso for logistic
 regression. J Roy Stat Soc B 70, 53–71.
- Meinshausen, N., Bühlmann, P., 2006. High-dimensional graphs and variable
 selection with the Lasso. Ann Stat 34, 1436–1462.
- Meinshausen, N., Bühlmann, P., 2010. Stability selection (with discussion).
 J Roy Stat Soc B 72, 417–473.
- Nicodemus, K.N., Malley, J.D., Strobl, C., Ziegler, A., 2010. The bahaviour
 of Random Forest permutation-based variable importance measures under
 predictor correlation. BMC Bioinformatics 11.
- ⁷³⁹ Politis, D.N., Romano, J.P., Wolf, M., 1999. Subsampling. Springer, Berlin.
- R Development Core Team, 2011. R: A Language and Environment for
 Statistical Computing. R Foundation for Statistical Computing. Vienna,
 Austria. ISBN 3-900051-07-0.
- Ravikumar, P., Wainwright, M.J., Lafferty, J.D., 2010. High-dimensional Ising model selection using ℓ_1 -regularized logistic regression. Ann Stat 38, 1287–1319.

Reinhardt, J.D., Fellinghauer, B., Strobl, R., Stucki, G., 2010. Dimension reduction in human functioning and disability outcomes research: Graphical
models versus principal components analysis. Disabil Rehabil 32, 1000–
1010.

- Reinhardt, J.D., Mansmann, U., Fellinghauer, B., Strobl, R., Grill, E., von
 Elm, E., Stucki, G., 2011. Functioning and disability in people living with
 spinal cord injury in high- and low-resourced countries: A comparative
 analysis of 14 countries. Int J Public Health 56, 341–352.
- Royston, P., Altman, D.G., Sauerbrei, W., 2006. Dichotomizing continuous
 predictors in multiple regression: A bad idea. Stat Med 25, 127–141.
- Snookes, S.H., Gunn, J.K., Eldridge, B.J., Donath, S.M., Hunt, R. W. Galea,
 M.P., Shekerdemian, L., 2010. A systematic review of motor and cognitive
 outcomes after early surgery for congenital heart disease. Pediatrics 125,
 818–27.
- Stekhoven, D.J., Bühlmann, P., 2011. MissForest nonparametric missing
 value imputation for mixed-type data. Preprint. arXiv: 1106.2068v1 .
- ⁷⁶² Storni, M., 2011. Enquêtes, sources: Enquête suisse sur la santé. Office
 ⁷⁶³ Fédéral de la Statistique, Neuchâtel.
- Strobl, C., Boulesteix, A.L., Kneib, T., Augustin, T., Zeileis, A., 2008. Conditional variable importance for Random Forests. BMC Bioinformatics
 9.
- Strobl, C., Boulesteix, A.L., Zeileis, A., Hothorn, T., 2007. Bias in Random
 Forest variable importance measures: Illustrations, sources and a solution.
 BMC Bioinformatics 8.
- Strobl, R., Stucki, G., Grill, E., Müller, M., Mansmann, U., 2009. Graphical models illustrated complex associations between variables describing
 human functioning. J Clin Epidemiol 62, 922–933.
- Stucki, G., Kostanjsek, N., Ustün, B., Cieza, A., 2008. ICF-based classification and measurement of functioning. Eur J Phys Rehabil Med 44,
 315–328.

- Tibshirani, R., 1996. Regression shrinkage and selection via the Lasso. J
 Roy Stat Soc B 58, 267–288.
- TNO, 2004. TNO-AZL pre-school children quality of life users manual. TNO
 PG, Leiden, Netherlands, 2004. TNO-PG, Leiden, Netherlands.
- von Rhein, M., Dimitropoulos, A., Valsangiacomo Buechel, E.R., Landolt,
 M.A., Latal, B., . Risk factors for neurodevelopmental impairments in
 school-age children after cardiac surgery with full-flow cardiopulmonary
 bypass. J Thorac Cardiov Sur , Mar 9. [Epub ahead of print].
- Watson, N., 2002. Well, I know this is going to sound very strange to you, but
 I don't see myself as a disabled person: Identity and disability. Disability
 & Society 17, 509–527.
- Whittaker, J., 1990. Graphical Models in Applied Multivariate Statistics.
 John Wiley & Sons, Inc., New Jersey.
- WHO, 2001. International Classification of Functioning, Disability and
 Health (ICF). WHO Press, Geneva.
- WHO and The World Bank, 2011. World Report on Disability. WHO Press,
 Geneva.
- Yu, H., 2010. Rmpi: Interface (Wrapper) to MPI (Message-Passing Interface).