1 Some general and historical remarks on the types of model

Graphical models aim to describe in concise form the possibly complex interrelations between a set of variables so that key properties can be read directly off a graph. The central idea is that each variable is represented by a node in a graph. Any pair of nodes may become coupled, that is joined by an edge. Coupled nodes are also said to be adjacent. For many types of graph, a missing edge represents some form of conditional independence between the pair of variables and an edge present can be interpreted as a corresponding conditional dependence. Because the conditioning set may be empty, or may contain some or all of the other variables, a variety of types of graph have been developed and are used to represent different types of structure.

A particularly important distinction is between directed and undirected edges. In the former an arrow indicates the direction of dependence of a response on an explanatory variable, the latter is also called a regressor. If, on the other hand, two variables are to be interpreted on an equal standing then the edge between them is typically undirected. For instance, systolic and diastolic blood pressure are treated as being on equal standing because they are two aspects of a single phenomenon, namely a blood pressure wave.

Graphical Markov models started to be developed after 1970 as special subclasses of log-linear models for contingency tables and of joint Gaussian distributions, where conditioning for each variable is in both situations on all of the other variables; see Darroch et al. (1980), Wermuth (1976, 1980). These models are typically represented by undirected graphs with edges that are full lines. The same types of graph were used by the physicist Gibbs (1902) to describe for two systems of particles having the same node sets, one as more complex whenever its nodes have more edges, that is larger numbers of ‘nearest neighbors’.

The first extension was to problems in which the variables can be arranged recursively, that is in an ordered sequence, so that each variable turns into a single response to variables in its past and may be explanatory only to other variables in its future; see Wermuth (1980), Wermuth & Lauritzen (1983). This led for only single responses to what are now called directed acyclic graphs, for sequences of joint or single responses to the so-called regression graphs and to distributions said to be generated over graphs.
For such generated Gaussian distributions, these models include as a subclass the path analyses of the geneticist Wright (1923, 1934). Wright had studied sequences of exclusively linear regressions as possible stepwise generating processes for his data. In his graphs, each missing arrow corresponds to the vanishing of the partial correlation coefficient given all remaining variables in the past of a given response, which in Gaussian distributions is a conditional independence constraint. For other types of generated distributions, an important issue is to identify parametric consequences of conditional independences; for instance for so-called CG-regressions see Lauritzen & Wermuth (1989), Edwards & Lauritzen (2001).

In general, the vanishing of a correlation coefficient may coexist with a nonlinear dependence. Conversely, a substantial partial correlation can occur in spite of conditional independence; for an example see Wermuth & Cox (1998). Currently, one knows also for jointly symmetric binary variables generated over a directed acyclic graph, that an arrow vanishes in the graph if and only if there is a corresponding zero partial correlation; see Wermuth, Cox & Marchetti (2009). Zero partial correlations given all other variables may reflect conditional independences more generally, provided the distribution is generated over even more specialized types of graph; see Loh & Wainwright (2013), Wermuth, Marchetti & Zwiernik (2014), Wermuth & Marchetti (2014).

Next extensions were to variables of any type so that a missing edge corresponds to a conditional independence. This exploits a proposal by the probabilist Markov (1912) that many types of seemingly complex distribution may be strongly simplified by conditional independences. Important issues were defining sets of independences for a graph and criteria to derive all implied independences so that the independence structure captured by the graph becomes well understood; see here Section 4 below.

Further developments include different types of chain graph models; see Cox & Wermuth (1993), Drton (2009). The name ‘chain graph’ reflects that there is a full ordering of the variables into a sequence of joint or single responses and possibly a set of remaining variables that is to capture the context of a study or properties of individuals under study given at the baseline. For parameterizations of Gaussian distributions with different types of chain graph see Wermuth, Wiedenbeck & Cox (2006).

Statistical monographs documenting the early development of what are now called graphical Markov models are by Whittaker (1990), Edwards (1995), Lauritzen (1996), Cox & Wermuth (1996). For surveys of probabilistic aspects see Pearl (1988) and
Special theoretical results, not touched upon here, have been derived under the assumption that a given probability distribution satisfies all independence constraints represented by a graph and no more. Such distributions have been said to be ‘faithful to the graph’; see Spirtes, Glymour & Scheines (1993). It is important to know that faithful distributions exist in a given family of distributions: one can then choose a member at random and it captures precisely the independence structure of the graph. But such an existence is of little relevance for data analyses, in which some parameters are essentially known because, say, the direction and strength of some dependences result from substantive theory or from previous empirical studies. For an ‘unfaithful family’ of Gaussian distributions see Wermuth (2012), Section 2.5.

2 Sequences of regressions and data generating processes

Directed acyclic graphs are a common subclass of all currently known types of chain graph. Distributions generated over a directed acyclic graph result in a stepwise fashion in terms of univariate conditional distributions, also called recursive single-response regressions. These may be compatible with causal interpretations and therefore appear at first sight attractive for substantive research that is driven by causal hypotheses.

It is however well understood, from randomized clinical trials in particular, that proper interventions often result in modifying more than a single response. For instance, a medication that is to reduce blood pressure, will typically affect both, systolic and diastolic pressure. Hence, models that are to be compatible with causal interpretations should contain response variables that may respond at the same time to a change in relevant explanatory variables, such as it is possible with joint response regressions.

Nevertheless, much of the current literature on causal modeling is based on directed acyclic graphs and on only virtual interventions; see Pearl (2009, 2014). With such a virtual intervention, changes in a single response are recorded that result by fixing the values of some variables, say the treatments, and by removing arrows pointing to these variables in a given graph. Implicit is the assumption that a given joint family of distribution remains unchanged, otherwise.

These recorded changes in virtual interventions, even though they are often called ‘causal effects’, may tell next to nothing about actual effects in proper interventions with,
for instance, completely randomized allocations of patients to treatments. Typically, several proper interventions are needed to gain trust in the estimated effects to be nearly stable under a reasonable range of conditions, in addition to other types of study and convincing theoretical explanations. Then, one may have successfully identified causes in complex real-world contexts.

Sequences of regressions in joint and single responses are the most attractive chain graph models for observational as well as intervention studies. For them, residual associations among the responses may often be regarded as secondary features. But, standard univariate estimation methods for regression coefficients may lead to distorted estimates whenever two associated joint responses on equal standing have disjoint subsets of regressors, a situation that has become known as seemingly unrelated regressions. When strong residual dependences remain after one has been regressing each response component separately on two different sets of regressors, then distorted parameter estimates may result, see Haavelmo (1943), Zellner (1963), Drton & Richardson (2004).

For all other known types of chain graph than regression graph, recursive generating processes may not exist since single response components are conditioned on other joint responses on equal standing. While substantive theory may occasionally support such models, this type of conditioning is typically counterintuitive whenever one main aim of an analysis is to identify early predictors for responses. But now, graphical criteria are available to decide whether the regression graph of a given sequence of joint or single regressions, defines the same independence structure as another chain graph, that is whether they are Markov equivalent; see Wermuth & Sadeghi (2012), Section 7.

For applications, the arguably most important recent developments concern conditions under which the regression graph can be used to trace development, to predict implied dependences in addition to implied independences, as well as graphical criteria for possible confounding effects when some variables are ignored or subpopulations are studied. Throughout, symbol ⊥ means independence and symbol ⊶ means dependence.

3 Regression graphs as partial summaries of data analyses

We give here two examples of data to which corresponding detailed statistical analyses have been published; see the Appendix in Wermuth & Sadeghi (2012) for the first and the Appendix in Wermuth & Cox (2013) for the second set of data.

In the regression graphs derived for both examples, the dashed lines capture re-
main associations among two joint responses and full lines for the context variables, reflect that conditioning is on all the context variables simultaneously. Estimation is for both data sets by local modeling of each response alone on its past and of response pairs on the union of their directly explanatory variables. When there are only independence constraints concerning responses and no seemingly unrelated regressions, local maximum-likelihood (m.l) estimates lead directly to proper m.l. estimates for the joint distribution; see Cox (2006) for such types of general principle.

In both of the following examples, data analyses lead to traceable regressions; see Wermuth (2012). This means that for a given ordered sequences of single and joint responses, the resulting regression graph permits not only to read off independences, but more importantly for most applications, sequences of directed edges show pathways of development.

Tracing of paths is always possible for joint Gaussian distributions whenever each edge in its regression graph represents a substantial conditional dependence; see here Section 4. This may not be possible with graphs of some structural equation models; see Wermuth (1992). More importantly, sufficient conditions for traceability using just the graph, are now known for other types of distributions generated over regression graphs.

Data on chronic pain treatment

For some data with a medical research question, Figure 1 shows a first ordering of the variables, derived by physicians and statisticians prior to the analyses.

![Figure 1: Initial ordering of variables in the chronic pain study for a sequence of regressions. Variables within a same box are treated on an equal standing. Variables in any one box are considered conditionally given all variables their past, listed within boxes to their right.](image-url)
We are grateful to Judith Kappesser, now Department of Psychology, Liebig-University of Giessen, for letting us use her data. They are for 201 chronic pain patients who have been given a three-week stationary treatment at a chronic pain clinic. Two main research questions are: which development is most influential for success or failure of treatment and is it necessary to include information on the patient’s site of main pain?

The response of primary interest is self-reported success of treatment, measured three months after discharge by a score of several aspects of the illness. The context variables, which capture features that cannot be modified, were here age, gender, lower or higher level of formal schooling, number of previous other illnesses and duration of pain.

There are a number of intermediate variables. Before and after a three-week stationary treatment, questionnaire scores are available of depression and of intensity of pain ranging from ‘no pain’ to ‘pain as strong as imaginable’. The chronification score incorporates different aspects, such as time since onset of pain, spreading of pain, use of pain relievers, the patient’s pain treatment history. Main site of pain has here two categories: ‘back pain’ and pain on the ‘head, face, or neck’.

The regression graph of Figure 2 summarizes some aspects of the statistical analyses.

![Diagram](image)

Figure 2: Well-fitting sequences of regressions which have a statistically significant relations for each edge present in the graph. Discrete variables are drawn as dots, continuous ones as circles. For instance, the two context variables are marginally independent, written as $B \perp V$ and response $Z_b$ is conditionally independent of $V$ given $A, B, U$; $Z_b \perp V | A, B, U$, also $A$ is marginally dependent on $B$, written as $A \not\perp B$, while $U$ depends on $V$ given $A$: $U \not\perp V | A$.

**Note:** Full arrows in regression graphs are sometimes also drawn as dashed-line arrows and dashed lines as so-called arcs, which are full lines with arrow-heads at both ends.

The graph shows in particular which of the variables are needed for each response so that for any given response, adding one more of the potentially explanatory variables
does not improve prediction. Site of pain is an important intermediate variable since it is a node along a direction-preserving path of arrows pointing from level of schooling to treatment success, hence should be part of any future study of chronic pain.

Some of the directions and type of dependences, which cannot be read off the graph, are as follows. Patients with many years of formal schooling (13 years or more) are more likely to be head-pain patients, the others are more likely to be back-pain patients, possibly because more of them have jobs involving heavy physical work. Back-pain patients have higher scores of pain chronicity, reach higher stages of intensity of pain before treatment and report higher intensity of pain after treatment.

Never captured by the graph are nonlinear dependences, here of \( Y \) on \( Z_a \). Treatment success, \( Y \), is low whenever higher intensity of pain levels remain after treatment, \( Z_a \). But at relatively lower levels of \( Z_a \), treatment is clearly the more successful the lower the intensity of pain at discharge, \( Z_a \).

For these data, checking for nonlinear relations and for interactive effects did not point to other important relations. The model fits the data well since for each response taken separately, no indication was found that adding further variables, further nonlinear or interactive effects would improve prediction and no strong dependences remained among the residuals of the joint responses on equal standing.

One important path of development is that patients with shorter formal schooling are more likely to get chronic back-pain and patients with chronic back-pain get help too late and respond less well to the type of treatment offered in the chronic pain clinic. This suggests as possible interventions to modify the type of treatment for the back-pain patients or to raise the general level of formal schooling.

**Data on child development**

Here, we use for data of 347 families participating in the ‘Mannheim study of children at risk’. We are grateful to Manfred Laucht, Central Institute of Mental Health, Mannheim, for permitting a reanalysis of the data.

The study started with a random sample of more than 100 newborns from the general population of children born near Mannheim in Germany. This sample was completed to give roughly equal subsamples, in each of nine level combinations of the two types of adversity at birth, categorized to be at levels ‘no, moderate or high’; see Laucht, Esser & Schmidt (1997). In other words, there was heavy oversampling of children at risk for later motoric or cognitive deficits and observations were taken at the same time for a
norm group of children in the same region.

The recruitment of families stopped with 362 children. All measurements were reported in standardized form using the mean and standard deviation of the starting random sample. Of the 362 German-speaking families who entered the study when their first, single child was born without malformations or any other severe handicap, 347 families still participated when their child reached the age of 8 years. There are joint responses of main and of secondary interest at age 8 and at age 4 years. Each of these contains two components of possible deficits: cognitive or motoric.

One main difference to previous analyses is that we averaged three different assessments of each of two types of risk: recorded at birth, at 3 months and at two years. In both cases, this can be justified by the six observed pairwise correlations being all nearly equal; see e.g. Wermuth (2013). These averaged scores are risks at two years for motoric deficits, labelled \( X_r \), and for cognitive deficits, labelled \( Y_r \). Two possible additional risks were identified at three months after birth, a score called unprotective environment, \( E \), and a binary variable \( H \), which records whether the child had to be hospitalized during the first three months after birth. There are clearly recognizable, strong dependences corresponding to each arrow present in Figure 3.

\[
\begin{align*}
Y_8: & \quad Y_4 + X_4^2 + E + H \\
X_8: & \quad X_4^2 + X_r \\
Y_4: & \quad Y_r + X_r^2 \\
Y_r: & \quad E^2 \\
X_r: & \quad E + H
\end{align*}
\]

**Note:** In this notation supplementing the graph, every square term implies that also a main effect is included in a regression; see McCullagh and Nelder (1983).

The graph shows in particular for motoric deficits at age eight years of the child, \( X_8 \), no arrows are pointing to it from risks at 3 months, \( E, H \), or from any variable for...
the cognitive side, $Y_8, Y_4, Y_r$ given information on the more recent motoric deficit, $X_4$ and the risk for motoric deficits, $X_r$. By contrast, cognitive deficits at age 8 years, $Y_8$ depend directly on unprotective environment at 3 months, on being hospitalized up to 3 months, as well as on motoric deficits at 2 years, given both more recent deficits, $Y_4, X_4$.

The coding of variables implies that all dependences are positive so that deficits accumulate with each additional regressor. Some of the effects are accelerated compared to merely linear dependences. This is not reflected in the graph alone but in Wilkinson’s notation added to the graph, as shown in Figure 4.

4 Questions regarding applications and statistical research

Here, we first list questions that arise in general when new statistical models are applied. We then give partial answers and references for sequences of regressions.

(i) Are case studies available in which the new models have been used fruitfully?

(ii) Can well-fitting models be derived from data and be tested as hypotheses formulated for future data?

(iii) What additional possibilities do the models offer to gain better insight into given research questions, especially to an understanding of development over time?

To (i), case studies with sequences of regressions, which include joint responses, continue to accumulate. In addition to the two examples summarized here in the previous section; see for instance Cox & Wermuth (1996), Cheung & Andersen (2003), Hardt et al. (2004), Smith (2009), Hardt, Herke & Schier (2011), Marchetti et al. (2011), Schier et al. (2014), Solis-Trapala et al. (2014).

To (ii), one most attractive feature of sequences of regressions is that their fitting requires typically no new estimation techniques. Standard methods are often sufficient; for linear regressions see Weisberg (2014), for categorical responses see Cox (1972), McCullagh & Nelder (1989), Andersen & Skovgaard (2010). To screen for nonlinear or interactive effects see Cox & Wermuth (1994). Regression graphs represent hypotheses about generating processes which can be tested in future studies.

When seemingly unrelated regressions are hypothesized, direct estimation methods are based for discrete variables on generalized linear models; see Marchetti and Lupparelli (2011), for joint Gaussian distributions, estimation is possible with structural equation models; see e.g. Bollen (1989). But as mentioned before, when strong residual
dependences remain in Gaussian seemingly unrelated regressions, especially for small
sample sizes, estimates may be far from the population values.

One may also regard seemingly unrelated regressions as so-called reduced models and
embed them in larger so-called covering models for which estimation is again standard;
see Cox & Wermuth (1990). Often m.l. estimates in the covering model are not far
from those obtained by separate regressions and are then good approximations to the
m.l. estimates in the reduced model.

To (iii), quite a number of new results have been obtained in the last years. We will
concentrate on the following few:

a) graphical conditions for the Markov equivalence of two regression graphs to be used
for possible alternative interpretations or for different types of fitting algorithm,

b) conditions and criteria for deriving implied independences and implied dependences
from a given regression graph,

c) ways of deciding on different types of confounding implied by a generating process
when some variables are unobserved, that is marginalized over, or a population
subgroup is studied, that is there is conditioning on the levels of some variables
present in the generating process.

Markov equivalence of regression graphs

Two different graphs are Markov equivalent if they define the same independence struc-
ture. The independence structure of a regression graph, with a given set of nodes and an
ordering for the responses, is determined by its list of missing edges for node pairs \( i, k \).
Such a graph has possibly three types of edge, full lines between context nodes, arrows
starting at a regressor and pointing to a response, and dashed lines between responses
on equal standing; see Figure 1 to recall the meaning of these terms.

A missing full \( i, k \)-line between two context nodes means conditional independence
given all remaining context nodes, a missing \( i, k \)-arrow pointing from \( k \) to \( i \) means
conditional independence given all other nodes in the past of \( i \) except for \( k \) and a
missing dashed \( i, k \)-line between two response nodes on equal standing means conditional
independence given other nodes in the past of \( i \) and \( k \).

A V-configuration in such a graph, often called just a V, consists of any three nodes
with two uncoupled nodes, called the outer nodes, and with two edges present that are
coupled to a common neighbor, called the inner node. There are two types of $V$s in regression graphs, named collision and transmitting $V$s. The possible collision $V$s are

$$i \leftarrow o \rightarrow k, \quad i \rightarrow o \leftarrow k, \quad i \leftarrow o \leftarrow k,$$

and all of the possible five others are the transmitting $V$s.

Directed acyclic graphs consist exclusively of arrows so that there can be only the middle $V$ above, where two uncoupled regressors point to a common response. Graphs of only full lines, often called concentration graphs, have no collision $V$s, while in graphs of only dashed lines, often called covariance graphs, every $V$ is of the collision type.

These latter two types of graph are subclasses of regression graphs and their names derive from parameterisations in joint Gaussian distributions. For such a distribution, zero off-diagonal elements in the covariance matrix, $\sigma_{ik}$, capture marginal independence, and zero off-diagonal elements in the concentration matrix, $\sigma^{ik}$, in the inverse of the covariance matrix, capture conditional independence given all the remaining nodes.

Two different types of regression graphs, which have the same node set and the same set of missing edges but different types of edge for some node pairs, are Markov equivalent if and only if their sets of collision $V$s coincide even though for any given $V$, there may be any of the three types of collision $V$s above; for a proof see Wermuth and Sadeghi (2012). One example is shown in Figure 4.

Figure 4: A regression graph that is Markov equivalent to a concentration graph.

The graph on the left of Figure 4 resulted from a retrospective study, with more variables than reported here. Questions about their childhood were answered by 283 adult females when visiting a general practitioner for some minor health problems; see Hardt (2008). No nonlinear or interactive effects were detected.

The well-fitting graph contains two binary variables, level of formal schooling and severe sexual abuse during childhood, and three quantitative measurements. Age in years is recorded directly, the other variables being derived from questionnaires. Family status indicates the recalled social standing of the family during early childhood. Family distress includes psychological disturbances and alcohol or drug problems of the parents.
From the Markov equivalence to the concentration graph on the right of Figure 4, one knows for instance directly that sexual abuse is independent of the level of formal schooling given knowledge about the family status. This implication may be derived from the defining independences of the graph on the left or be based on the following separation result in graph theory. If in an undirected graph with three disjoint subsets $\alpha, \beta, c$ of the given set of nodes, every path between $\alpha$ and $\beta$ has a node in $c$, then $\alpha$ is separated from $\beta$ by $c$, that is removal of set $c$ leaves $\alpha$ and $\beta$ disconnected. For concentration graphs, this separation implies $\alpha \perp \perp \beta | c$; see e.g. Lauritzen et al. (1990).

Figure 5 shows instead a regression graph on the left that is Markov equivalent to a covariance graph. It is the simplest case of the seemingly unrelated regressions with regressors labelled 3, 4 and responses labelled 1, 2. For instance, it follows from the graph definitions that edge 1--2 means $1 \not \perp \perp 2 | 3, 4$ on the left and $1 \not \perp \perp 2$ on the right.

As discussed in the next section, to transfer such equivalence results for graphs to a distribution generated over a regression graph, this distribution has to mimic some properties of joint Gaussian distributions; see also Wermuth and Sadeghi (2012).

**Deciding on implied independences**

The work on reading all implied independences off a directed acyclic graph started with a path-braking, complex theorem, called d-separation; see Pearl (1988), Geiger, Verma & Pearl (1990). For the reduction of d-separation to the above described separation criterion for undirected graphs; see Lauritzen et al. (1990).

A third criterion is based on matrix representations of graphs, named their edge matrices. Square edge matrices contain zeros for missing edges, ones for edges present and ones along the diagonal to extend the graph theoretic notion of adjacency matrices in such a way that some sums or products of edge matrices describe transformations of graphs; see Wermuth, Wiedenbeck & Cox (2006). It gives the most direct criterion in that it leads to a matrix with the dimensions of two disjoint node subsets $\alpha$ and $\beta$: if this is a matrix of zeros only, then it is established that the graph implies a desired conditional independence.
In particular, let four disjoint subsets $\alpha, \beta, c, m$ partition the node set of a directed acyclic graph, let further $a = \alpha \cup m$, and $b = \alpha \cup c$, then the transformation to the edge matrix $\mathcal{P}_{a \mid b}$ parallels the transformation of parameters in linear sequences of single-response regressions to the matrix $\Pi_{a \mid b}$ of least-squares regression coefficients with $Y_a$ as response and $Y_b$ as regressor. For joint Gaussian distributions, the submatrix of $\Pi_{a \mid b}$ for rows $\alpha$ and columns $\beta$ is zero, $\Pi_{a \mid \beta, c} = 0$, if and only if $\alpha \perp \perp \beta \mid c$. In general, $\mathcal{P}_{a \mid \beta, c}$, the corresponding submatrix of $\mathcal{P}_{a \mid b}$ is zero if the given graph implies $\alpha \perp \perp \beta \mid c$. The three types of criteria have been proven to be equivalent; see Marchetti & Wermuth (2009). For combining independences for sequences of regressions, the generated distribution also has to satisfy conditions that mimic some properties of Gaussian distributions.

Properties of joint Gaussian distributions have been nicely summarized in the information theory literature, together with other properties that hold for all probability distributions; see Lněníčka and Matúš (2007), Definition 1. To combine independence statements in sequences of regressions, conditional independences have to combine downward, named also presence of the intersection property, and marginal independences have to combine upwards, in addition, named also presence of the composition property; see Sadeghi and Lauritzen (2014).

Sufficient for the intersection property are strictly positive distributions; see San Martin, Mouchard & Rolin (2005) for extensions. Sufficient for the composition property is that to every nonlinear effect there is also a linear one and that to every interactive effect there are also substantial main effects; see Németh and Rudas (2013) for an example when this property does not hold in a sociological context. In such an instance, models more complex than graphical models are needed, such as those included for discrete variables in the class of marginal models; see Bergsma and Rudas (2002).

An illustration of the two properties is given for just three nodes $i, h, k$ in Figure 6. On the left is a complete regression graph with joint response $\{h, k\}$, on the right a complete directed acyclic graph with the single responses ordered as $(i, h, k)$.

Figure 6: Two regression graphs where removal of the $hi$-edge and the $ki$-edge leads to $i \perp \perp h, k$, provided independences combine upward (left) and downward (right).
Deciding on implied dependences

Edge matrix results for directed acyclic graphs have been extended to the more general types of regression graph and, more importantly, to inferring that a generating regression graph implies the conditional dependence \( \alpha \mathcal{R} \beta | c \) if \( \mathcal{P}_{\alpha | \beta, c} \neq 0 \); see Wermuth (2012).

To permit conclusions about dependences for sequences of regressions, the generated distribution has to have, in addition, non-vanishing parameters to each edge present in the graph and it has to be dependence-inducing, a property also called singleton transitivity. Distributions with all above mentioned properties have been called traceable, since their regression graph can be used to study pathways of development. Prediction of the strength or direction of induced associations may vary with the used measures of dependence; see Jiang, Ding & Geng (2014).

For trivariate Gaussian distributions, there are already several types of possible parameters: covariances, concentrations and regression coefficients which all have nice recursive properties. A detailed notation is needed to understand their relations:

\[
\begin{align*}
\sigma_{123} &= \sigma_{12} - \sigma_{13}\sigma_{23}/\sigma_{33}, \\
n23.1 &= \sigma_{23} - \sigma_{12}\sigma_{13}/\sigma_{33}, \\
\beta_{1|3} &= \beta_{1|3,2} + \beta_{1|2,3}\beta_{2|3},
\end{align*}
\]

where \( \sigma_{123} \) denotes the conditional covariance of 1, 2 given 3; see Anderson (1958), \( \sigma_{23.1} \) the concentration of 2, 3 marginalized over 1; see Dempster (1969), and \( \beta_{1|3,2} \) the population coefficient of 2 when regressing 1 on both 2 and 3; see Cochran (1938).

The right-hand sides of the above equations contain the Gaussian parameters for dependence in graphs with three nodes. These parameters are in equation (1) for a covariance graph, in equation (2) for a concentration graph and in equation (3) for a directed acyclic graph: with 1 as response to 2, 3 and 2 as a response to 3; see Figure 8.

The coefficient of 3 when regressing 1 only on 3, denoted by \( \beta_{1|3} \) can be regarded as the result of two paths: of \( \beta_{1|3,2} \), an arrow pointing from 3 to 1, and of a sequence of two arrows starting at 3 and pointing to 1 via 2 with effect \( \beta_{1|2,3}\beta_{2|3} \). Sometimes, the first is called the direct effect of 3 on 1, the second the indirect effect and \( \beta_{1|3} \) the overall effect.

If for instance \( 0 = \sigma_{12} = \sigma_{13} \) in equation (1), then \( \sigma_{123} = 0 \) and consequently also \( \beta_{1|3,2} = 0 \) in equation (3) so that 1 has no dependence on 2 and 3 jointly. This is the Gaussian case of the more general notion of combining independences upwards. The
latter is written explicitly for three variables as

\[(1 \perp \perp 2 \text{ and } 1 \perp \perp 3) \implies 1 \perp \perp 2, 3.\]

With more variables, the equations (1) to (3) generalize, by adding everywhere a larger conditioning set in equations (1) and (3), to get, for instance, \(\sigma_{12|c}, \sigma_{12|3c} \text{ and } \beta_{1|3,c}, \beta_{1|3,2c}\), and by adding a larger marginalizing set in equation 2 to get \(\sigma_{23,m}, \sigma_{23,1m}\).

The three measures of dependence relate for a node set consisting of 1, 2, 3, c, m as

\[\beta_{1|3,c} = \frac{\sigma_{13|c}/\sigma_{33|c}}{-\sigma_{33}} = -\frac{\sigma_{13,m}/\sigma_{11,m}}{\sigma_{22}},\]

derived via the sweep operator by Dempster (1969), and explaining above why 0 = \(\sigma_{12|3} = \beta_{1|2,3}\) and 0 = \(\sigma_{23,1} = \beta_{2|3}\) when all variances such as \(\sigma_{33|c}\) and all precisions, such as \(\sigma_{11,m}\), are nonzero in the two single-response regressions.

For joint Gaussian distributions, the dependence-inducing property can be proven in its simplest form using equation (1): for \(1 \perp \perp 3\) and \(2 \perp \perp 3\), one may have at most \(\sigma_{12|3} = 0\) or \(\sigma_{1|2} = 0\) but never both. In the case of \(\sigma_{12|3} = 0\), the induced correlation, \(\rho_{12} = \sigma_{12}/\sqrt{\sigma_{11}\sigma_{22}}\), has also been named a ‘spurious correlation’ since the dependence between the two variables 1 and 2 can be ‘explained away’ by conditioning on their common neighbor 3. For three variables, the dependence-inducing property is:

\[(1 \perp \perp 3 \text{ and } 2 \perp \perp 3) \implies 1 \perp \perp 2|3 \text{ or } 1 \perp \perp 2 \text{ but never both.}\]

It has been proven that binary variables are also dependence inducing; see Simpson (1951). But there are constellations of counts for which both independences \(1 \perp \perp 2|3\) and \(1 \perp \perp 2\) seem to hold and a decision would have to be based on outside information.

**Independence-predicting and independence-preserving graphs**

The results for deciding on implied independences and dependences, based on an induced edge matrix, have been extended to derive regression graphs implied by a given generating process when, for instance, the order of the responses or the conditioning sets or the marginalizing sets are changed; see Wermuth & Cox (2004).

Then the so-called independence-predicting graphs, may be derived by using the partial closure operator (Wermuth, Wiedenbeck & Cox, 2006) as well as sums and products of edge matrices, but each of these operations has also an intuitive translation into closing special types of paths in graphs; see Wermuth (2012).
For instance, when in another study, the same variables were available except for cognitive deficits after 4 years, $Y_8$, $Y_4$, one predicts from the starting graph in Figure 4 and an unchanged order of the remaining variables, the regression graph in Figure 7. In this case, it is just a subgraph of Figure 4 obtained by removing nodes and edges of $Y_8$ and $Y_4$, no additional dependences are induced.

Figure 7: The regression graph induced by Figure 3 after marginalizing over $Y_8$ and $Y_4$.

By contrast, when $X_8$ and $X_4$ are not available, all remaining variables turn to be directly explanatory for $Y_8$. One consequence of this finding is that it is more important for psychologists and psychiatrists to evaluate also motor development than it is for physicians to take also cognitive development into account.

Typically, one cannot use such an induced regression graph to condition on or marginalize over more nodes and still see what the starting graph would have implied for this case, while this is possible with the so-called independence-preserving graphs. Starting from directed acyclic graphs, three types of such graphs have been proposed, the MC-graphs by Koster (2002), the maximal ancestral graphs by Richardson and Spirtes (2002) and the summary graphs by Wermuth (2011). For their relations and proofs of Markov equivalence see Sadeghi (2013). To construct these types of graph within the program environment R see Sadeghi and Marchetti (2012).

Summary graphs may be derived for the more general regression graphs and, if obtained after marginalizing only, they provide graphical criteria to detect confounding.

Graphical representations of distortions

For traceable regressions, the regression graph represents an independence structure and a partly specified dependence structure. The graph can be viewed as a hypothesis of how sequences of single or joint responses generate a joint distribution when, for instance, corresponding point estimates of parameters are taken as the population values. For reliable interpretations of estimated effects, it is important to prevent, if at all possible, any important sources of sizeable distortions of the actual population parameters.
Different types of distortions of a treatment effect may be avoided by using regression graphs and appropriate study designs. To see this, we show in Figure 8 simple cases of under-conditioning, of over-conditioning and of direct confounding by using a node crossed by two lines, $\emptyset$, to indicate that the variable is to be marginalized over and a node surrounded by a square, $\square$, to indicate that the variable is to be conditioned on.

For instance, by using label 3 for treatment and label 1 for the outcome or response to 2 and 3, the graph on the left of Figure 8 shows one important intermediate variable, labelled 2, which could be, say, high compliance of the patients for lower doses and lower or no compliance for higher doses of the treatment. After ignoring such differential compliance, a distorted overall effect results which then coincides with the result of a so-called intention-to-treat analysis. Conditioning on the common response in the middle graph distorts the simple dependence of 2 on 3 and is also named a selection bias. More complex cases of such over-conditioning may occur, for instance, when there is an effect for $2 \prec 3$ and, in addition, a path like $2 \prec \emptyset \prec 3$.

Figure 8: Left: under-conditioning for $1 \nmid 3 \mid 2$ by ignoring an intermediate variable, middle: over-conditioning for $2 \nmid 3$ by selecting levels of the common response 1 and right: direct confounding for $1 \nmid 2 \mid 3$ by ignoring the common explanatory variable 3 for 1 and 2; generating a double edge $1 \prec 2$ in the summary graph obtained by marginalizing over node 3.

The simplest case of direct confounding, shown on the right of Figure 8 is also called the presence of an unmeasured confounder. It has a longer history than graphical models; see Vandenbroucke (2002). It is avoided when there is a successful, fully randomized allocation of individuals to treatment levels since in that case, all effects on treatment, observed or unobserved, are removed. This design leads also to a removal of all incoming arrows to the treatment variable in a regression graph and to the absence of any double edge in corresponding summary graphs, where the only possible double edge is $\circ \prec \circ$.

Another source of distortion, named indirect confounding, may lead to strong dependence reversal compared to the population dependence; see Wermuth and Cox (2008). A first example is due to Robins and Wasserman (1997), shown here in Figure 9, left. Notice that in this regression graph there are no unmeasured confounders of $Y \prec T_p$. 
and there is no over-conditioning and no under-conditioning for this dependence of $Y$ on $T_p$. But $A$ is intermediate between $Y$ and $T_p$. By conditioning on just the regressors $T_r$ and $T_p$ of $Y$ that remain when $U$ is unobserved, one conditions implicitly also on their past, hence on $A$ and thereby activates the path $Y \rightarrow A \leftarrow X_p$ and distorts the conditional dependence $Y \perp T_p | T_r, U$ as it is present in the generating graph.

![Diagram]

Figure 9: Left: full randomization for $T_p$ leads to removal of $T_p \leftarrow U$, randomized allocation of individuals to selected levels of a more recent treatment, $T_r$, given results of the intermediate outcome $A$, leads to removal of $T_r \leftarrow U$ and of $T_r \leftarrow T_p$ and to the presence of $T_r \leftarrow A$; right: the summary graph obtained by marginalizing over $U$; path $Y \rightarrow A \leftarrow T_p$ explaining the indirect confounding of $Y \leftarrow T_p$ when response $Y$ is regressed on only $T_p$ and $T_r$.

More generally, indirect confounding will result for $Y \leftarrow T$ in a regression graph, when in the summary graph obtained after marginalizing over all unobserved variables, one or more of the following two types of paths are present; see Wermuth (2011):

$$Y \leftarrow \cdots \cdots \leftarrow T \quad \text{or} \quad Y \leftarrow \cdots \cdots \cdots \leftarrow T,$$

where every inner node along the path is an intermediate variable between $Y$ and $T$ and $\cdots$ denotes a possible continuation of the same type of neighboring edges.

Indirect confounding, which can be much stronger than direct confounding, appears to have been largely ignored so far in the literature, not only in the statistical one, but also in the current literature on causal modeling, based on virtual interventions using directed acyclic graphs or structural equations; see Pearl (2014), Richardson and Robins (2013). Only direct confounding and selection bias are frequently considered.

The specification of generating processes via sequences of single or joint response regressions lead to regression graphs that may be needed for useful causal interpretations and to corresponding summary graphs that help to avoid possible mistaken interpretations when some variables are hidden, that is latent or unobserved.
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**Abstract:** We describe how graphical Markov models started to emerge in the last 40 years, based on three essential concepts that had been developed independently more than a century ago. Sequences of joint or single regressions and their regression graphs are singled out as being best suited for analyzing longitudinal data and for tracing developmental pathways. Interpretations are illustrated using two sets of data and some of the more recent, important results for sequences of regressions are summarized.

**Keywords:** Composition property, Conditional independence, Dependence-inducing distributions, Direct confounding, Independence-predicting graphs, Independence-preserving graphs, Indirect confounding, Intersection property, Intervention studies, Issues of causality, Longitudinal studies, Markov equivalence, Observational studies, Regression graphs, Separation criteria.

**Relevant ms-codes:** 42172, 42159, 42153, 42142, 42095, 42036, 1847, 4126, 1146, 1153