# **12**

# Introduction to Graphical Modelling

Marco Scutari <sup>1</sup> and Korbinian Strimmer <sup>2</sup>

- <sup>1</sup> Genetics Institute, University College London (UCL), London, UK
- <sup>2</sup> Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig, Germany

The aim of this chapter is twofold. In the first part (Sections 12.1, 12.2 and 12.3) we will provide a brief overview of the mathematical and statistical foundations of graphical models, along with their fundamental properties, estimation and basic inference procedures. In particular we will develop Markov networks (also known as Markov random fields) and Bayesian networks, which are the subjects of most past and current literature on graphical models. In the second part (Section 12.4) we will review some applications of graphical models in systems biology.

#### 12.1 Graphical Structures and Random Variables

Graphical models are a class of statistical models which combine the rigour of a probabilistic approach with the intuitive representation of relationships given by graphs. They are composed by two parts:

- 1. a set  $\mathbf{X} = \{X_1, X_2, \dots, X_p\}$  of *random variables* describing the quantities of interest. The statistical distribution of  $\mathbf{X}$  is called the *global distribution* of the data, while the components it factorises into are called *local distributions*.
- 2. a graph  $\mathcal{G} = (\mathbf{V}, E)$  in which each vertex  $v \in \mathbf{V}$ , also called a node, is associated with one of the random variables in  $\mathbf{X}$  (they are usually referred to interchangeably). Edges  $e \in E$ , also called links, are used to express the dependence structure of the data (the set of dependence relationships among

the variables in **X**) with different semantics for *undirected graphs* (Diestel 2005) and *directed acyclic graphs* (Bang-Jensen and Gutin 2009).

The scope of this class of models and the versatility of its definition are well expressed by Pearl (1988) in his seminal work 'Probabilistic Reasoning in Intelligent Systems: Networks of Plausible Inference':

Graph representations meet our earlier requirements of explicitness, saliency, and stability. The links in the graph permit us to express directly and quantitatively the dependence relationships, and the graph topology displays these relationships explicitly and preserves them, under any assignment of numerical parameters.

The nature of the link outlined above between the dependence structure of the data and its graphical representation is given again by Pearl (1988) in terms of *conditional* independence (denoted with  $\perp \!\!\! \perp_{P}$ ) and graphical separation (denoted with  $\perp \!\!\! \perp_{G}$ ).

**Definition 12.1.1** A graph  $\mathcal{G}$  is a dependency map (or D-map) of the probabilistic dependence structure P of  $\mathbf{X}$  if there is a one-to-one correspondence between the random variables in  $\mathbf{X}$  and the nodes  $\mathbf{V}$  of  $\mathcal{G}$ , such that for all disjoint subsets  $\mathbf{A}$ ,  $\mathbf{B}$ ,  $\mathbf{C}$  of  $\mathbf{X}$  we have

$$\mathbf{A} \perp_{P} \mathbf{B} \mid \mathbf{C} \Longrightarrow \mathbf{A} \perp_{G} \mathbf{B} \mid \mathbf{C}. \tag{12.1}$$

Similarly, G is an independency map (or I-map) of P if

$$\mathbf{A} \perp_{P} \mathbf{B} \mid \mathbf{C} \longleftarrow \mathbf{A} \perp_{G} \mathbf{B} \mid \mathbf{C}. \tag{12.2}$$

 ${\cal G}$  is said to be a perfect map of P if it is both a D-map and an I-map, that is

$$\mathbf{A} \perp_{P} \mathbf{B} \mid \mathbf{C} \iff \mathbf{A} \perp_{G} \mathbf{B} \mid \mathbf{C}, \tag{12.3}$$

and in this case P is said to be isomorphic to G.

Note that this definition does not depend on a particular characterisation of graphical separation, and therefore on the type of graph used in the graphical model. In fact both Markov networks (Whittaker 1990) and Bayesian networks (Pearl 1988), which are by far the two most common classes of graphical models treated in literature, are defined as minimal I-maps even though the former use undirected graphs an the latter use directed acyclic graphs. Minimality requires that, if the dependence structure P of  $\mathbf{X}$  can be expressed by multiple graphs, we must use the one with the minimum number of edges; if any further edge is removed then the graph is no longer an I-map of P. Being an I-map guarantees that two disjoint sets of nodes  $\mathbf{A}$  and  $\mathbf{B}$  found to be separated by  $\mathbf{C}$  in the graph (according to the characterisation of separation for that type of graph) correspond to independent sets of variables. However, this does not mean that every conditional independence relationship present in P is reflected in the graph; this is true only if the graph is also assumed to be a dependency map, making it a perfect map of P.

In Markov networks graphical separation (which is called undirected separation or *u-separation* in Castillo et al. (1997)) is easily defined due to the lack of direction of the links.

**Definition 12.1.2** If A, B and C are three disjoint subsets of nodes in an undirected graph G, then C is said to separate A from B, denoted  $A \perp_G B \mid C$ , if every path between a node in A and a node in B contains at least one node in C.

In Bayesian networks separation takes the name of directed separation (or d-separation) and is defined as follows (Korb and Nicholson 2009).

**Definition 12.1.3** If A, B and C are three disjoint subsets of nodes in a directed acyclic graph  $\mathcal{G}$ , then C is said to d-separate A from B, denoted A  $\perp \!\!\! \perp_G B \mid C$ , if along every path between a node in A and a node in B there is a node v satisfying one of the following two conditions:

- 1. v has converging edges (i.e. there are two edges pointing to v from the adjacent nodes in the path) and none of v or its descendants (i.e. the nodes that can be reached from v) are in  $\mathbb{C}$ .
- 2. v is in  $\mathbf{C}$  and does not have converging edges.

A simple application of these definitions is illustrated in Figure 12.1. We can see that in the undirected graph on the top A and B are separated by C, because there is no edge between A and B and the path that connects them contains C; so we can conclude that A is independent from B given C according to Definition 12.1.2. As for three directed acyclic graphs, which are called the converging, serial and diverging connections, we can see that only the last two satisfy the conditions stated in Definition 12.1.3. In the converging connection C has two incoming edges (which violates the second condition) and is included in the set of nodes we are conditioning on (which violates the first condition). Therefore we can conclude that C does not d-separate A and B and that according to the definition of I-map we can not say that A is independent from B given C.

A fundamental result descending from the definitions of separation and d-separation is the Markov property (or Markov condition), which defines the decomposition of the global distribution of the data into a set of local distributions. For Bayesian networks it is related to the chain rule of probability (Korb and Nicholson 2009); it takes the form

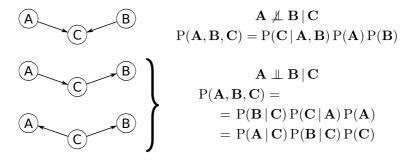
P(**X**) = 
$$\prod_{i=1}^{p} P(X_i | \Pi_{X_i})$$
 for discrete data and (12.4)
$$f(\mathbf{X}) = \prod_{i=1}^{p} f(X_i | \Pi_{X_i})$$
 for continuous data, (12.5)

$$f(\mathbf{X}) = \prod_{i=1}^{P} f(X_i | \Pi_{X_i})$$
 for continuous data, (12.5)

so that each local distribution is associated with a single node  $X_i$  and depends only on the joint distribution of its parents  $\Pi_{X_i}$ . This decomposition holds for any separation (undirected graphs)

$$\begin{array}{c}
\mathbf{A} \perp \mathbf{B} \mid \mathbf{C} \\
\mathbf{P}(\mathbf{A}, \mathbf{B}, \mathbf{C}) = \mathbf{P}(\mathbf{A} \mid \mathbf{C}) \mathbf{P}(\mathbf{B} \mid \mathbf{C}) \mathbf{P}(\mathbf{C})
\end{array}$$

d-separation (directed acyclic graphs)



**Figure 12.1** Graphical separation, conditional independence and probability factorisation for some simple undirected and directed acyclic graphs. The undirected graph is a simple 3 node chain, while the directed acyclic graphs are the *converging*, *serial* and *diverging connections* (collectively known as *fundamental connections* in the theory of Bayesian networks).

Bayesian network, regardless of its graph structure. In Markov networks on the other hand local distributions are associated with the *cliques* (maximal subsets of nodes in which each element is adjacent to all the others)  $C_1$ ,  $C_2$ , ...,  $C_k$  present in the graph; so

$$P(\mathbf{X}) = \prod_{i=1}^{k} \psi_i(\mathbf{C}_i)$$
 for discrete data and (12.6)

$$f(\mathbf{X}) = \prod_{i=1}^{k} \psi_i(\mathbf{C}_i)$$
 for continuous data. (12.7)

The functions  $\psi_1, \psi_2, \dots, \psi_k$  are called *Gibbs' potentials* (Pearl 1988), *factor potentials* (Castillo et al. 1997) or simply *potentials*, and are non-negative functions representing the relative mass of probability of each clique. They are proper probability or density functions only when the graph is *decomposable* or *triangulated*, that is when it contains no induced cycles other than triangles. With any other type of graph inference becomes very hard, if possible at all, because  $\psi_1, \psi_2, \dots, \psi_k$  have no direct statistical interpretation. Decomposable graphs are also called *chordal* (Diestel 2005) because any cycle of length at least four has a

chord (a link between two nodes in a cycle that is not contained in the cycle itself). In this case the global distribution factorises again according to the chain rule and can be written as

$$P(\mathbf{X}) = \frac{\prod_{i=1}^{k} P(\mathbf{C}_i)}{\prod_{i=1}^{k} P(\mathbf{S}_i)}$$
 for discrete data and (12.8)

$$f(\mathbf{X}) = \frac{\prod_{i=1}^{k} f(\mathbf{C}_i)}{\prod_{i=1}^{k} f(\mathbf{S}_i)}$$
 for continuous data, (12.9)

where  $S_i$  are the nodes of  $C_i$  which are also part of any other clique up to  $C_{i-1}$  (Pearl 1988).

A trivial application of these factorisations is illustrated again in Figure 12.1. The Markov network is composed by two cliques,  $C_1 = \{A, C\}$  and  $C_2 = \{B, C\}$ , separated by  $R_1 = \{C\}$ . Therefore according to Equation 12.6 we have

$$P(\mathbf{X}) = \frac{P(A, C) P(B, C)}{P(C)} = P(A | C) P(B | C) P(C).$$
 (12.10)

In the Bayesian networks we can see that the decomposition of the global distribution results in three local distributions, one for each node. Each local distribution is conditional on the set of parents of that particular node. For example, in the converging connection we have that  $\Pi_A = \{\varnothing\}$ ,  $\Pi_B = \{\varnothing\}$  and  $\Pi_C = \{A, B\}$ , so according to Equation 12.4 the correct factorisation is

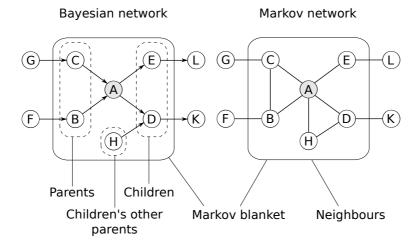
$$P(\mathbf{X}) = P(A) P(B) P(C \mid A, B). \tag{12.11}$$

On the other hand, in the serial connection we have that  $\Pi_A = \{\varnothing\}$ ,  $\Pi_B = \{C\}$  and  $\Pi_C = \{A\}$ , so

$$P(X) = P(A) P(C|A) P(B|C).$$
 (12.12)

The diverging connection can be shown to result in the same factorisation, even though the nodes have different sets of parents than in the serial connection.

Another fundamental result descending from the link between graphical separation and probabilistic independence is the definition of the Markov blanket (Pearl 1988) of a node  $X_i$ , the set that completely separates  $X_i$  from the rest of the graph. Generally speaking it is the set of nodes that includes all the knowledge needed to do inference on  $X_i$ , from estimation to hypothesis testing to prediction, because all the other nodes are conditionally independent from  $X_i$  given its Markov blanket. In Markov networks the Markov blanket coincides with the neighbours of  $X_i$  (all the nodes that are connected to  $X_i$  by an edge); in Bayesian networks it is the union of the children of  $X_i$ , its parents, and its children's other parents (see Figure 12.2). In both classes of models the usefulness of Markov blankets is limited by the sparseness of the network. If edges are few compared to the number of nodes the interpretation of each Markov blanket becomes a useful tool in understanding and predicting the behaviour of the data.



**Figure 12.2** The Markov blanket of the node A in a Bayesian network (on the left) and in the corresponding Markov network given by its *moral graph* (on the right). The two graphs express the same dependence structure, so the Markov blanket of A is the same.

The two characterisations of graphical separation and of the Markov properties presented above do not appear to be closely related, to the point that these two classes of graphical models seem to be very different in construction and interpretation. There are indeed dependency models that have an undirected perfect map but not a directed acyclic one, and vice versa (see Pearl (1988), pages 126 - 127 for a simple example of a dependency structure that cannot be represented as a Bayesian network). However, it can be shown (Castillo et al. 1997; Pearl 1988) that every dependency structure that can be expressed by a decomposable graph can be modelled both by a Markov network and a Bayesian network. This is clearly the case for the small networks shown in Figure 12.2, as the undirected graph obtained from the Bayesian network by moralisation (connecting parents which share a common child) is decomposable. It can also be shown that every dependency model expressible by an undirected graph is also expressible by a directed acyclic graph, with the addition of some auxiliary nodes. These two results indicate that there is a significant overlap between Markov and Bayesian networks, and that in many cases both can be used to the same effect.

#### 12.2 Learning Graphical Models

Fitting graphical models is called *learning*, a term borrowed from expert systems and artificial intelligence theory, and in general requires a two-step process.

The first step consists in finding the graph structure that encodes the conditional independencies present in the data. Ideally it should coincide with the minimal I-map of the global distribution, or it should at least identify a distribution

as close as possible to the correct one in the probability space. This step is called *network structure* or simply *structure learning* (Koller and Friedman 2009; Korb and Nicholson 2009), and is similar in approaches and terminology to model selection procedures for classical statistical models.

The second step is called *parameter learning* and, as the name suggests, deals with the estimation of the parameters of the global distribution. This task can be easily reduced to the estimation of the parameters of the local distributions because the network structure is known from the previous step.

Both structure and parameter learning are often performed using a combination of numerical algorithms and prior knowledge on the data. Even though significant progress have been made on performance and scalability of learning algorithms, an effective use of prior knowledge and relevant theoretical results can still speed up the learning process severalfold and improve the accuracy of the resulting model. Such a boost has been used in the past to overcome the limitations on computational power, leading to the development of the so-called *expert systems* (for real-world examples see the MUNIN (Andreassen et al. 1989), ALARM (Beinlich et al. 1989) and Hailfinder (Abramson et al. 1996) networks); it can still be used today to tackle larger and larger problems and obtain reliable results.

#### 12.2.1 Structure learning

Structure learning algorithms have seen a steady development over the past two decades thanks to the increased availability of computational power and the application of many results from probability, information and optimisation theory. Despite the (sometimes confusing) variety of theoretical backgrounds and terminology they can all be traced to only three approaches: constraint-based, scorebased and hybrid.

Constraint-based algorithms use statistical tests to learn conditional independence relationships (called *constraints* in this setting) from the data and assume that the graph underlying the probability distribution is a perfect map to determine the correct network structure. They have been developed originally for Bayesian networks, but have been recently applied to Markov networks as well (see for example the *Grow-Shrink* algorithm (Bromberg et al. 2009; Margaritis 2003), which works with minor modifications in both cases). Their main limitations are the lack of control of either the *family-wise error rate* (Dudoit and van der Laan 2007) or the *false discovery rate* (Efron 2008) and the additional assumptions needed by the tests themselves, which are often asymptotic and with problematic regularity conditions.

Score-based algorithms are closer to model selection techniques developed in classical statistics and information theory. Each candidate network is assigned a score reflecting its goodness of fit, which is then taken as an objective function to maximise. Since the number of both undirected graphs and directed acyclic graphs grows more than exponentially in the number of nodes (Harary and Palmer 1973) an exhaustive search is not feasible in all but the most trivial cases. This has led to an extensive use of heuristic optimisation algorithms, from local search (starting

from an initial network and changing one edge at a time) to genetic algorithms (Russell and Norvig 2009). Convergence to a global maximum however is not guaranteed, as they can get stuck into a local maximum because of the noise present in the data or a poor choice in the tuning parameters of the score function.

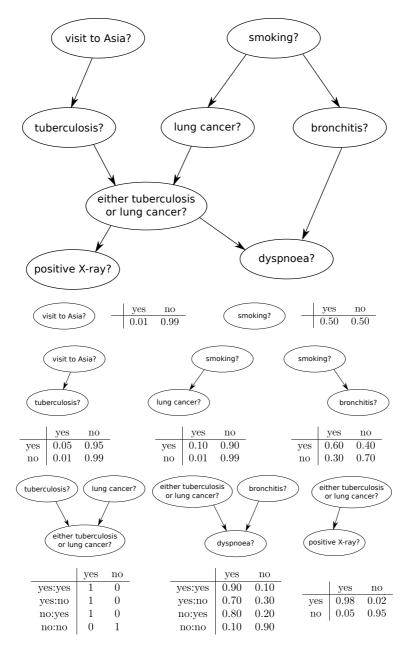
Hybrid algorithms use both statistical tests and score functions, combining the previous two families of algorithms. The general approach is described for Bayesian networks in Friedman et al. (1999b), and has proved one of the top performers up to date in Tsamardinos et al. (2006). Conditional independence tests are used to learn at least part of the conditional independence relationships from the data, thus restricting the search space for a subsequent score-based search. The latter determines which edges are actually present in the graph and, in the case of Bayesian networks, their direction.

All these structure learning algorithms operate under a set of common assumptions, which are similar for Bayesian and Markov networks:

- there must be a one-to-one correspondence between the nodes of the graph and the random variables included in the model; this means in particular that there must not be multiple nodes which are functions of a single variable.
- there must be no unobserved (also called *latent* or *hidden*) variables that are parents of an observed node in a Bayesian network; otherwise only part of the dependency structure can be observed, and the model is likely to include spurious edges. Specific algorithms have been developed for this particular case, typically based on Bayesian posterior distributions or the EM algorithm (Dempster et al. 1977); see for example Friedman (1997), Elidan and Friedman (2005) and Binder et al. (1997).
- all the relationships between the variables in the network must be conditional independencies, because they are by definition the only ones that can be expressed by graphical models.
- every combination of the possible values of the variables in X must represent
  a valid, observable (even if really unlikely) event. This assumption implies
  a strictly positive global distribution, which is needed to have uniquely
  determined Markov blankets and, therefore, a uniquely identifiable model.
  Constraint-based algorithms work even when this is not true, because the
  existence of a perfect map is also a sufficient condition for the uniqueness
  of the Markov blankets (Pearl 1988).

Some additional assumptions are needed to properly define the global distribution of  $\mathbf{X}$  and to have a tractable, closed-form decomposition:

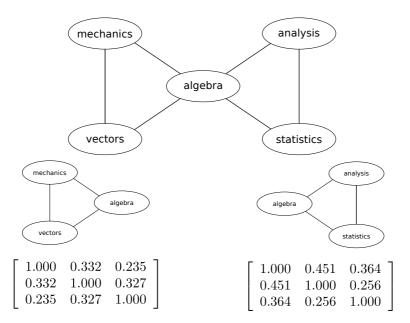
• observations must be stochastically independent. If some form of temporal or spatial dependence is present it must be specifically accounted for in the definition of the network, as in *dynamic Bayesian networks* (Koller and Friedman 2009). They will be covered in Section 12.4.4 and Chapter 12.



**Figure 12.3** Factorisation of the ASIA Bayesian network from Lauritzen and Spiegelhalter (1988) into local distributions, each with his own conditional probability table. Each row contains the probabilities conditional on a particular configuration of parents.

- if all the random variables in **X** are discrete or categorical both the global and the local distributions are assumed to be *multinomial*. This is by far the most common assumption in literature, at least for Bayesian networks, because of its strong ties with the analysis of contingency tables (Agresti 2002; Bishop et al. 2007) and because it allows an easy representation of local distributions as *conditional probability tables* (see Figure 12.3).
- if on the other hand all the variables in X are continuous the global distribution is usually assumed to follow a *multivariate Gaussian distribution*, and the local distributions are either *univariate* or *multivariate Gaussian distributions*. This assumption defines a subclass of graphical models called *graphical Gaussian models* (GGMs), which overlaps both Markov (Whittaker 1990) and Bayesian networks (Neapolitan 2004). A classical example from Edwards (2000) is illustrated in Figure 12.4.
- if both continuous and categorical variables are present in the data there are three possible choices: assuming a *mixture* or *conditional Gaussian distribution* (Bøttcher 2004; Edwards 2000), discretising continuous attributes (Friedman and Goldszmidt 1996) or using a nonparametric approach (Bach and Jordan 2003).

The form of the probability or density function chosen for the local distributions



**Figure 12.4** The MARKS Graphical Gaussian network from Edwards (2000) and its decomposition into cliques, the latter characterised by their partial correlation matrices.

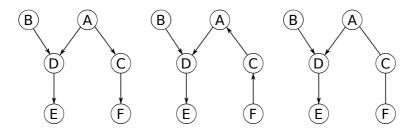
determines which score functions (for score-based algorithms) or conditional independence tests (for constraint-based algorithms) can be used by structure learning algorithms. Common choices for conditional independence tests are:

- discrete data: Pearson's  $\chi^2$  and the  $G^2$  tests (Agresti 2002; Edwards 2000), either as asymptotic or permutation tests. The  $G^2$  test is actually a log-likelihood ratio test (Lehmann and Romano 2005) and is equivalent to mutual information tests (Cover and Thomas 2006) up to a constant.
- *continuous data*: Student's t, Fisher's Z and the log-likelihood ratio tests based on partial correlation coefficients (Legendre 2000; Neapolitan 2004), again either as asymptotic or permutation tests. The log-likelihood ratio test is equivalent to the corresponding mutual information test as before.

Score functions commonly used in both cases are penalised likelihood scores such as the *Akaike* and *Bayesian Information criteria* (AIC and BIC, see Akaike (1974) and Schwarz (1978) respectively), posterior densities such as the *Bayesian Dirichlet* and *Gaussian equivalent* scores (BDe and BGe, see Heckerman et al. (1995) and Geiger and Heckerman (1994) respectively) and entropy-based measures such as the *Minimum Description Length* (MDL) by Rissanen (2007).

The last important property of structure learning algorithms, one that sometimes is not explicitly stated, is their inability to discriminate between *score equivalent* Bayesian networks (Chickering 1995). Such models have the same *skeleton* (the undirected graph resulting from ignoring the direction of every edge) and the same *v-structures* (another name for the converging connection illustrated in Figure 12.1), and therefore they encode the same conditional independence relationships because every d-separation statement that is true for one of them also holds for all the others.

This characterisation implies a partitioning of the space of the possible networks into a set of equivalence classes whose elements are all I-maps of the same probability distribution. The elements of each of those equivalence classes are indistinguishable from each other without additional information, such as a non-uniform prior distribution; their factorisations into local distributions are equivalent.



**Figure 12.5** Two score equivalent Bayesian networks (on the left and in the middle) and the partially directed graph representing the equivalence class they belong to (on the right). Note that the direction of the edge  $D \to E$  is set because its reverse  $E \to D$  would introduce two additional v-structures in the graph; for this reason it is called a *compelled edge* (Pearl 1988).

Statistical tests and almost all score functions (which are in turn called *score equivalent functions*), including those detailed above, are likewise unable to choose one model over an equivalent one. This means that learning algorithms, which base their decisions on these very tests and scores, are only able to learn which equivalence class the minimal I-map of the dependence structure belongs to. They are usually not able to uniquely determine the direction of all the edges present in the network, which is then represented as a partially directed graph (see Figure 12.5).

#### 12.2.2 Parameter learning

Once the structure of the network has been learned from the data the task of estimating and updating the parameters of the global distribution is greatly simplified by the application of the Markov property.

Local distributions in practise involve only a small number of variables; furthermore their dimension usually does not scale with the size of  $\mathbf{X}$  (and is often assumed to be bounded by a constant when computing the computational complexity of algorithms), thus avoiding the so called *curse of dimensionality*. This means that each local distribution has a comparatively small number of parameters to estimate from the sample, and that estimates are more accurate due to the better ratio between the size of parameter space and the sample size.

The number of parameters needed to uniquely identify the global distribution, which is the sum of the number of parameters of the local ones, is also reduced because the conditional independence relationships encoded in the network structure fix large parts of the parameter space. For example in graphical Gaussian models partial correlation coefficients involving (conditionally) independent variables are equal to zero by definition, and joint frequencies factorise into marginal ones in multinomial distributions.

However, parameter estimation is still problematic in many situations. For example it is increasingly common to have sample size much smaller than the number of variables included in the model; this is typical of microarray data, which have a few tens or hundreds observations and thousands of genes. Such a situation, which is called "small n, large p", leads to estimates with high variability unless particular care is taken both in structure and parameter learning (Castelo and Roverato 2006; Hastie et al. 2009; Schäfer and Strimmer 2005a).

Dense networks, which have a high number of edges compared their nodes, represent another significant challenge. Exact inference quickly becomes unfeasible as the number of nodes increases, and even approximate procedures based on Monte Carlo simulations and bootstrap resampling require large computational resources (Koller and Friedman 2009; Korb and Nicholson 2009). Numerical problems stemming from floating point approximations (Goldberg 1991) and approximate numerical algorithms (such as the ones used in matrix inversion and eigenvalue computation) should also be taken into account.

## 12.3 Inference on Graphical Models

Inference procedures for graphical models focus mainly on *evidence propagation* and model validation, even though other aspects such as robustness (Cozman 1997) and sensitivity analysis (Gómez-Villegas et al. 2008) have been studied for specific settings.

Evidence propagation (another term borrowed from expert systems literature) studies the impact of new evidence and beliefs on the parameters of the model. For this reason it is also referred to as *belief propagation* or *belief updating* (Castillo et al. 1997; Pearl 1988), and has a clear Bayesian interpretation in terms of posterior and conditional probabilities. The structure of the network is usually considered fixed, thus allowing a scalable and efficient updating of the model through its decomposition into local distributions.

In practise new evidence is introduced by either altering the relevant parameters (soft evidence) or setting one or more variables to a fixed value (hard evidence). The former can be thought of as a model revision or parameter tuning process, while the latter is carried out by conditioning the behaviour of the network on the values of some nodes. The process of computing such conditional probabilities is also known as conditional probability query on a set of query nodes (Koller and Friedman 2009), and can be performed with a wide selection of exact and approximate inference algorithms. Two classical examples of exact algorithms are variable elimination (optionally applied to the clique tree form of the network) and Kim and Pearl's Message Passing algorithm. Approximate algorithms on the other hand rely on various forms of Monte Carlo sampling such as forward sampling (also called logic sampling for Bayesian networks), likelihood-weighted sampling and importance sampling. Markov Chain Monte Carlo methods such as Gibbs sampling are also widely used (Korb and Nicholson 2009).

Model validation on the other hand deals with the assessment of the performance of a graphical model when dealing with new or existing data. Common measures are the goodness-of-fit scores cited in the Section 12.2.1 or any appropriate loss measure such as misclassification error (for discrete data) and the residual sum of squares (for continuous data). Their estimation is usually carried out using either a separate testing data set or cross validation (Koller and Friedman 2009; Peña et al. 2005) to avoid negatively biased results.

Another nontrivial problem is to determine the confidence level for particular structural features. In Friedman et al. (1999a) this is accomplished by learning a large number of Bayesian networks from bootstrap samples drawn from the original data set and estimating the empirical frequency of the features of interest. Scutari (2011) has recently extended this approach to obtain some univariate measures of variability and perform some basic hypothesis testing. Both techniques can be applied to Markov networks with little to no change. Tian and He (2009) on the other hand used a non-uniform prior distribution on the space of the possible structures to compute the exact marginal posterior distribution of the features of interest.

## 12.4 Application of Graphical Models in Systems Biology

In *systems biology* graphical models are employed to describe and to identify interdependencies among genes and gene products, with the eventual aim to better understand the molecular mechanisms of the cell. In *medical systems biology* the specific focus lies on disease mechanisms mediated by changes in the network structure. For example, a general assumption in cancer genomics is that there are different active pathways in healthy compared to affected tissues.

A common problem in the practical application of graphical models in systems biology is the high dimensionality of the data compared to the small sample size. In other words, there are a large number p of variables to be considered whereas the number of observations n is small due to ethical reasons and cost factors. Typically, the number of parameters in a graphical model grows with some power of the number of variables. Hence, if the number of genes is large, the parameters describing the graphical model (e.g. edge probabilities) quickly outnumber the data points. For this reason graphical modelling in systems biology almost always requires some form of regularised inference, such as Bayesian inference, penalised maximum likelihood or other shrinkage procedures.

#### 12.4.1 Correlation networks

The simplest graphical models used in systems biology are *relevance networks* (Butte et al. 2000), which are also known in statistics as *correlation graphs*. Relevance networks are constructed by first estimating the correlation matrix for all p(p-1)/2 pairs of genes. Subsequently, the correlation matrix is thresholded at some prespecified level, say at  $|r_{ij}| < 0.8$ , so that weak correlations are set to zero. Finally, a graph is drawn in order to depict the remaining strong correlations.

Technically, correlation graphs visualise the *marginal* (in)dependence structure of the data. Assuming the latter are normally distributed, a missing edge between two genes in a relevance network is indicative of marginal stochastic independence. Because of their simplicity, both in terms of interpretation as well as computation, correlation graphs are enormously popular, not only for analysing gene expression profiles but also many other kinds of omics data (Steuer 2006).

#### 12.4.2 Covariance selection networks

The simplest graphical model that considers conditional rather than marginal dependencies is the *covariance selection model* (Dempster 1972), also known as *concentration graph* or *graphical Gaussian model* (Whittaker 1990). In a GGM the graph structure is constructed in the same way as in a relevance network; the only difference is that the presence of an edge is determined by the value of the corresponding *partial correlation* (the correlation between any two genes once the linear effect all other p-2 genes has been removed) instead of the marginal correlation used above. Partial correlations may be computed in a number

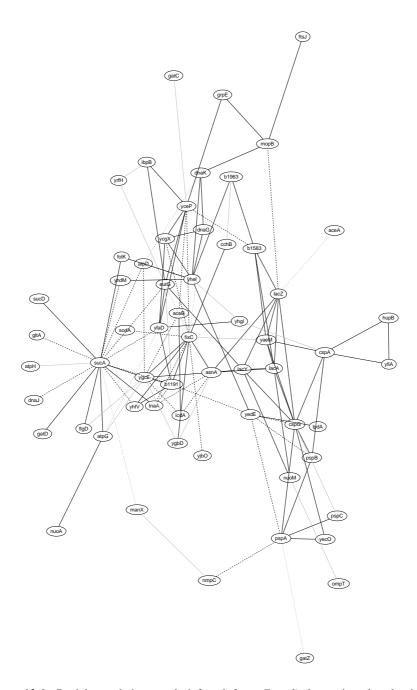
of ways, but the most direct approach is by inversion and subsequent standardisation of the correlation matrix (the inverse of the covariance matrix is often called a *concentration matrix*). Specifically, it can be shown that if an entry in the inverse correlation matrix is close to zero then the partial correlation between the two corresponding genes also vanishes. Thus, under the normal data assumption a missing edge in a GGM implies conditional independence.

Partial correlation graphs derived from genomic data are often called *gene association networks*, to distinguish them from correlation-based relevance networks. Despite their mathematical simplicity, it is not trivial to learn GGMs from high-dimensional "small n, large p" genomic data (Schäfer and Strimmer 2005c). There are two key problems. First, inferring a large-scale correlation (or covariance) matrix from relatively few data is an ill-posed problem that requires some sort of regularisation. Otherwise the correlation matrix is singular and therefore cannot be inverted to compute partial correlations. Second, an effective variable selection procedure is needed to determine which estimated partial correlations are not significant and which represent actual linear dependencies. Typically, GGM model selection involves assumptions concerning the sparsity of the actual biological network.

The first applications of covariance selection models to genome data were either restricted to a small number of variables (Waddell and Kishino 2000), used as a preprocessing step in cluster analysis to reduce the effective dimension of the model (Toh and Horimoto 2002), or employed low order partial correlations as an approximation to fully conditioned partial correlations (de la Fuente et al. 2004). However, newer inference procedures for GGMs are directly applicable to highdimensional data. A Bayesian regression-based approach to learn large-scale GGMs is given in Dobra et al. (2004). Schäfer and Strimmer (2005b) introduced a largescale model selection procedure for GGMs using false discovery rate multiple testing with an empirically estimated null model. Schäfer and Strimmer (2005a) also proposed a James-Stein-type shrinkage correlation estimator that is both computationally and statistically efficient even in larger dimensions, specifically for use in network inference. An example of a GGM reconstructed with this algorithm from E. coli data is shown in Figure 12.6. Methods for estimating large-scale inverse correlation matrices using different variants of penalised maximum likelihood are discussed by Li and Gui (2006), Banerjee et al. (2008) and Friedman et al. (2008). Most recently, Andrei and Kendziorski (2009) considered a modified GGM that allows the specification of interactions (i.e. multiplicative dependencies) among genes, and Krämer et al. (2009) conducted an extensive comparison of regularised estimation techniques for GGMs.

#### 12.4.3 Bayesian networks

Both gene relevance and gene association networks are undirected graphs. In order to learn about directed conditional dependencies Bayesian network inference procedures have been developed for static (and later also for time course) microarray



**Figure 12.6** Partial correlation graph inferred from *E. coli* data using the algorithm described in Schäfer and Strimmer (2005b) and Schäfer and Strimmer (2005a). Dotted edges indicate negative partial correlation.

data.

The application of Bayesian networks to learn large-scale directed graphs from microarray data was pioneered by Friedman et al. (2000), and has also been reviewed more recently in Friedman (2004). The high dimensionality of the model means that inference procedures are usually unable to identify a single best Bayesian network, settling instead on a set of equally well behaved models. In addition, as discussed in Section 12.2.1, all Bayesian networks belonging to the same equivalence class have the same score and therefore cannot be distinguished on the basis of the probability distribution of the data. For this reason it is often important to incorporate prior biological knowledge into the inference process of a Bayesian network. A Bayesian approach based on the use of informative prior distributions is described in Mukherjee and Speed (2008).

The efficiency of Bayesian networks, GGMs and relevance networks in recovering biological regulatory networks have been studied in an extensive and realistic setup in Werhli et al. (2006). Not surprisingly, the amount of information contained in gene expression and other high-dimensional data is often too low to allow for accurate reconstruction of all the details of a biological network. Nonetheless, both GGMs and Bayesian networks are able to elucidate some of the underlying structure.

# 12.4.4 Dynamic Bayesian networks

The extension of Bayesian networks to the analysis of time course data is provided by *dynamic Bayesian networks*, which explicitly account for time dependencies in their definition. The incorporation of temporal aspects is important for systems biology, as it allows to draw conclusions about causal relations.

Dynamic Bayesian networks are often restricted to linear systems, with two special (yet still very general) models: the vector-autoregressive (VAR) model and state-space models. The main difference between the two is that the latter includes hidden variables that are useful for implicit dimensionality reduction.

The VAR model was first applied to genomic data by Fujita et al. (2007) and Opgen-Rhein and Strimmer (2007b). A key problem of this kind of model is that it is very parameter-rich, and therefore it is hard to estimate efficiently and reliably. Opgen-Rhein and Strimmer (2007b) proposed a shrinkage approach whereas Fujita et al. (2007) employed lasso regression for sparse VAR modelling. A refinement of the latter approach based on the elastic net penalised regression is described in Shimamura et al. (2009). In all VAR models the estimated coefficients can be interpreted in terms of Granger causality (Opgen-Rhein and Strimmer 2007b).

State-space models are an extension of the VAR model, and include lower-dimensional latent variables to facilitate inference. The dimension of the latent variables is usually chosen in the order of the rank of the data matrix. Husmeier (2003), Perrin et al. (2003), and Rangel et al. (2004) were the first to study genomic data with dynamic Bayesian networks and to propose inference procedures suitable for use with microarray data. Bayesian learning procedures are discussed in

(Lähdesmäki and Shmulevich 2008). A general state-space framework that allows to model non-stationary time course data is given in Grzegorczyk and Husmeier (2009). Rau et al. (2010) present an empirical Bayes approach to learning dynamical Bayesian networks and apply it to gene expression data.

# 12.4.5 Other graphical models

Bayesian networks are graphical models where all edges are directed, whereas GGMs represent undirected conditional dependencies in multivariate data. On the other hand, *chain graphs* can include directed as well as undirected dependencies in same graph. One heuristic approach to infer an approximating chain graph from high-dimensional genomic data is described in Opgen-Rhein and Strimmer (2007a).

For reasons of simplicity, and to further reduce the number of parameters to be estimated, many graphical models used in systems biology only describe linear dependencies (GGM, VAR, state space models). Attempts to relax such linearity assumptions include entropy networks (Hausser and Strimmer 2009; Meyer et al. 2007) and copula-based approaches (Kim et al. 2008).

Finally, sometimes time-discrete models such as dynamic Bayesian networks are not appropriate to study the dynamics of molecular processes. In these cases stochastic differential equations (Wilkinson 2009) often represent a viable alternative. It is also important to keep in mind that, given the small sample size of omics data, the most complex graphical model is not necessarily the best choice for an analyst (Werhli et al. 2006).

#### References

Abramson B, Brown J, Edwards W, Murphy A and Winkler RL 1996 Hailfinder: A Bayesian System for Forecasting Severe Weather. *International Journal of Forecasting* 12(1), 57–71.

Agresti A 2002 Categorical Data Analysis 2nd edn. Wiley.

Akaike H 1974 A New Look at the Statistical Identification Model. IEEE Transactions on Automatic Control 19, 716–723.

Andreassen S, Jensen F, Andersen S, Falck B, Kjærulff U, Woldbye M, Sørensen A, Rosenfalck A and Jensen F 1989 MUNIN – An Expert EMG Assistant In *Computer-Aided Electromyography and Expert Systems* (ed. Desmedt JE) Elsevier pp. 255–277.

Andrei A and Kendziorski C 2009 An Efficient Method for Identifying Statistical Interactors in Gene Association Networks. *Biostatistics* **10**, 706–718.

Bach FR and Jordan MI 2003 Learning Graphical Models with Mercer Kernels In *Advances in Neural Information Processing Systems* (ed. Becker S, Thrun S and Obermayer K) vol. 15 MIT Press pp. 1009–1016.

Banerjee O, El Ghaoui L and d'Aspremont A 2008 Model Selection Through Sparse Maximum Likelihood Estimation for Multivariate Gaussian or Binary Data. *Journal of Machine Learning Resesearch* **9**, 485–516.

Bang-Jensen J and Gutin G 2009 Digraphs: Theory, Algorithms and Applications 2nd edn. Springer.

Beinlich I, Suermondt HJ, Chavez RM and Cooper GF 1989 The ALARM Monitoring System: A Case Study with Two Probabilistic Inference Techniques for Belief Networks *Proceedings of the 2nd European Conference on Artificial Intelligence in Medicine*, pp. 247–256. Springer-Verlag.

Binder J, Koller D, Russell S and Kanazawa K 1997 Adaptive Probabilistic Networks with Hidden Variables. *Machine Learning* **29**(2–3), 213–244.

Bishop YMM, Fienberg SE and Holland PW 2007 Discrete Multivariate Analysis: Theory and Practice. Springer.

Bøttcher SG 2004 Learning Bayesian Networks with Mixed Variables PhD thesis Department of Mathematical Sciences, Aalborg University.

Bromberg F, Margaritis D and Honavar V 2009 Efficient Markov Network Structure Discovery Using Independence Tests. *Journal of Artificial Intelligence Research* **35**, 449–485.

Butte AJ, Tamayo P, Slonim D, Golub TR and Kohane IS 2000 Discovering Functional Relationships Between RNA Expression and Chemotherapeutic Susceptibility Using Relevance Networks. PNAS 97, 12182–12186

Castelo R and Roverato A 2006 A Robust Procedure For Gaussian Graphical Model Search From Microarray Data With p Larger Than n. *Journal of Machine Learning Research* 7, 2621–2650.

Castillo E, Gutiérrez JM and Hadi AS 1997 Expert Systems and Probabilistic Network Models. Springer. Chickering DM 1995 A Transformational Characterization of Equivalent Bayesian Network Structures Proceedings of the 11th Conference on Uncertainty in Artificial Intelligence, pp. 87–98.

Cover TM and Thomas JA 2006 Elements of Information Theory 2nd edn. Wiley.

Cozman F 1997 Robustness Analysis of Bayesian Networks with Local Convex Sets of Distributions *Proceedings of the 13th Conference on Uncertainty in Artificial Intelligence*, pp. 108–11.

de la Fuente A, Bing N, Hoeschele I and Mendes P 2004 Discovery of Meaningful Associations in Genomic Data Using Partial Correlation Coefficients. *Bioinformatics* **20**, 3565–3574.

Dempster AP 1972 Covariance Selection. Biometrics 28, 157-175.

Dempster AP, Laird NM and Rubin DB 1977 Maximum Likelihood from Incomplete Data via the EM Algorithm. *Journal of the Royal Statistical Society Series B* 39, 1–39.

Diestel R 2005 Graph Theory 3rd edn. Springer.

Dobra A, Hans C, Jones B, Nevins JR, Yao G and West M 2004 Sparse Graphical Models for Exploring Gene Expression Data. *Journal of Multivariate Analysis* **90**, 196–212.

Dudoit S and van der Laan MJ 2007 Multiple Testing Procedures with Applications to Genomics. Springer.

Edwards DI 2000 Introduction to Graphical Modelling 2nd edn. Springer.

Efron B 2008 Microarrays, Empirical Bayes and the Two-Groups Model. *Statistical Science* **23**(1), 1–47. Elidan G and Friedman N 2005 Learning Hidden Variable Networks: The Information Bottleneck Approach. *Journal of Machine Learning Research* **6**, 81–127.

Friedman J, Hastie T and Tibshirani R 2008 Sparse Inverse Covariance Estimation with the Graphical Lasso. *Biostatistics* 9, 432–441.

Friedman N 1997 Learning belief networks in the presence of missing values and hidden variables Proceedings of the 14th International Conference on Machine Learning (ICML97), pp. 125–133.

Friedman N 2004 Inferring Cellular Networks Using Probabilistic Graphical Models. *Science* **303**, 799–805.

Friedman N and Goldszmidt M 1996 Discretizing Continuous Attributes While Learning Bayesian Networks *Proceedings of the 13th International Conference on Machine Learning (ICML96)*, pp. 157–165.

Friedman N, Goldszmidt M and Wyner A 1999a Data Analysis with Bayesian Networks: A Bootstrap Approach *Proceedings of the 15th Conference on Uncertainty in Artificial Intelligence*, pp. 206–215.

Friedman N, Linial M, Nachman I and Pe'er D 2000 Using Bayesian Networks to Analyze Gene Expression Data. *Journal of Computational Biology* **7**, 601–620.

Friedman N, Nachman I and Peér D 1999b Learning Bayesian Network Structure from Massive Datasets: The "Sparse Candidate" Algorithm *Proceedings of the 15th Conference on Uncertainty in Artificial Intelligence*, pp. 206–21.

Fujita A, Sato JR, Garay-Malpartida HM, Yamaguchi R, Miyano S, Sogayar MC and Ferreira CE 2007 Modeling Gene Expression Regulatory Networks with the Sparse Vector Autoregressive Model. BMC Systems Biology 1, 39.

Geiger D and Heckerman D 1994 Learning Gaussian Networks. Technical report, Microsoft Research. Available as Technical Report MSR-TR-94-10.

Goldberg D 1991 What Every Computer Scientist Should Know About Floating Point Arithmetic. ACM Computing Surveys 23(1), 5–48.

Gómez-Villegas MA, Maín P and Susi R 2008 Extreme inaccuracies in Gaussian Bayesian networks. *Journal of Multivariate Analysis* **99**(9), 1929–1940.

Grzegorczyk M and Husmeier D 2009 Non-Stationary Continuous Dynamic Bayesian Networks. Advances in Neural Information Processing Systems (NIPS) 22, 682–690.

Harary F and Palmer EM 1973 *Graphical Enumeration*. Academic Press.

Hastie T, Tibshirani R and Friedman J 2009 The Elements of Statistical Learning: Data Mining, Inference, and Prediction 2nd edn. Springer. Hausser J and Strimmer K 2009 Entropy Inference and the James-Stein Estimator, with Application to Nonlinear Gene Association Networks. *Journal of Machine Learning Resesearch* 10, 1469–1484.

Heckerman D, Geiger D and Chickering DM 1995 Learning Bayesian Networks: The Combination of Knowledge and Statistical Data. *Machine Learning* 20(3), 197–243. Available as Technical Report MSR-TR-94-09.

Husmeier D 2003 Sensitivity and Specificity of Inferring Genetic Regulatory Interactions from Microarray Experiments with Dynamic Bayesian Networks. Bioinformatics 19, 2271–2282.

Kim JM, Jung YS, Sungur EA, Han KH, Park C and Sohn I 2008 A Copula Method for Modeling Directional Dependence of Genes. *BMC Bioinformatics* **9**, 225.

Koller D and Friedman N 2009 *Probabilistic Graphical Models: Principles and Techniques*. MIT Press. Korb K and Nicholson A 2009 *Bayesian Artificial Intelligence* 2nd edn. Chapman and Hall.

Krämer N, Schäfer J and Boulesteix AL 2009 Regularized Estimation of Large-Scale Gene Association Networks using Graphical Gaussian Models. *BMC Bioinformatics* **10**, 384.

Lähdesmäki H and Shmulevich I 2008 Learning the Structure of Dynamic Bayesian Networks from Time Series and Steady State Measurements. Machine Learning 71, 185–217.

Lauritzen SL and Spiegelhalter D 1988 Local Computation with Probabilities on Graphical Structures and their Application to Expert Systems (with discussion). *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* **50**(2), 157–224.

Legendre P 2000 Comparison of Permutation Methods for the Partial Correlation and Partial Mantel Tests. *Journal of Statistical Computation and Simulation* **67**, 37–73.

Lehmann EL and Romano JP 2005 Testing Statistical Hypotheses 3rd edn. Springer.

Li H and Gui J 2006 Gradient Directed Regularization for Sparse Gaussian Concentration Graphs, with Applications to Inference of Genetic Networks. *Biostatistics* 7, 302–317.

Margaritis D 2003 Learning Bayesian Network Model Structure from Data PhD thesis School of Computer Science, Carnegie-Mellon University. Available as Technical Report CMU-CS-03-153.

Meyer PE, Kontos K, Lafitte F and Bontempi G 2007 Information-Theoretic Inference of Large Transcriptional Regulatory Networks. *EURASIP Journal on Bioinformatics and Systems Biology* **2007**, Article tID 79879, 9 pages.

Mukherjee S and Speed TP 2008 Network Inference using Informative Priors. *PNAS* **105**, 14313–14318. Neapolitan RE 2004 *Learning Bayesian Networks*. Prentice Hall.

Opgen-Rhein R and Strimmer K 2007a From Correlation to Causation Networks: a Simple Approximate Learning Algorithm and its Application to High-Dimensional Plant Gene Expression Data. *BMC Systems Biology* 1, 37.

Opgen-Rhein R and Strimmer K 2007b Learning Causal Networks from Systems Biology Time Course Data: an Effective Model Selection Procedure for the Vector Autoregressive Process. *BMC Bioinformatics* **8** (Suppl. 2), S3.

Pearl J 1988 Probabilistic Reasoning in Intelligent Systems: Networks of Plausible Inference. Morgan Kaufmann.

Peña JM, Börkegren J and Tegnér J 2005 Learning Dynamic Bayesian Network Models via Cross-Validation. Pattern Recognition Letters 26(14), 2295–2308.

Perrin BE, Ralaivola L, Mazurie A, Bottani S, Mallet J and d'Alché Buc F 2003 Gene Networks Inference Using Dynamic Bayesian Networks. *Bioinformatics* 19 (Suppl. 2), ii138–ii148.

Rangel C, Angus J, Ghahramani Z, Lioumi M, Sotheran E, Gaiba A, Wild DL and Falciani F 2004 Modeling T-Cell Activation Using Gene Expression Profiling and State Space Modeling. *Bioinformatics* 20, 1361–1372.

Rau A, Jaffrézic F, Foulley JL and Doerge RW 2010 An Empirical Bayesian Method for Estimating Biological Networks from Temporal Microarray Data. *Statistical Applications in Genetics and Molecular Biology* **9**(1), Article 9.

Rissanen J 2007 Information and Complexity in Statistical Modeling. Springer.

Russell SJ and Norvig P 2009 Artificial Intelligence: a Modern Approach 3rd edn. Prentice Hall.

Schäfer J and Strimmer K 2005a A Shrinkage Approach to Large-Scale Covariance Matrix Estimation and Implications for Functional Genomics. Statistical Applications in Genetics and Molecular Biology 4, 32.

Schäfer J and Strimmer K 2005b An Empirical Bayes Approach to Inferring Large-Scale Gene Association Networks. Bioinformatics 21, 754–764.

Schäfer J and Strimmer K 2005c Learning Large-Scale Graphical Gaussian Models from Genomic Data In *Science of Complex Networks: From Biology to the Internet and WWW* (ed. Mendes JFF, Dorogovtsev SN, Povolotsky A, Abreu FV and Oliveira JG), vol. 776, AIP Conference Proceedings, pp. 263–276. American Institute of Physics, Aveiro, PT, August 2004.

Schwarz G 1978 Estimating the Dimension of a Model. The Annals of Statistics 6(2), 461-464.

Scutari M 2011 Measures of Variability for Graphical Models PhD thesis School of Statistical Sciences, University of Padova.

Shimamura T, Imoto S, Yamaguchi R, Fujita A, Nagasaki M and Miyano S 2009 Recursive Regularization for Inferring Gene Networks from Time-Course Gene Expression Profiles. *BMC Systems Biology* 3, 41.

Steuer R 2006 On the Analysis and Interpretation of Correlations in Metabolomic Data. *Briefings in Bioinformatics* **151**, 151–158.

Tian J and He R 2009 Computing Posterior Probabilities of Structural Features in Bayesian Networks *Proceedings of the 25th Conference on Uncertainty in Artificial Intelligence*, pp. 538–547.

Toh H and Horimoto K 2002 Inference of a Genetic Network by a Combined Approach of Cluster Analysis and Graphical Gaussian Modeling. *Bioinformatics* 18, 287–297.

Tsamardinos I, Brown LE and Aliferis CF 2006 The Max-Min Hill-Climbing Bayesian Network Structure Learning Algorithm. *Machine Learning* **65**(1), 31–78.

Waddell PJ and Kishino H 2000 Cluster Inference Methods and Graphical Models Evaluated on NCI60 Microarray Gene Expression Data. *Genome Informatics* 11, 129–140.

Werhli AV, Grzegorczyk M and D.Husmeier 2006 Comparative Evaluation of Reverse Engineering Gene Regulatory Networks with Relevance Networks, Graphical Gaussian Models and Bayesian Networks. *Bioinformatics* **22**, 2523–2531.

Whittaker J 1990 Graphical Models in Applied Multivariate Statistics. Wiley.

Wilkinson DJ 2009 Stochastic Modelling for Quantitative Description of Heterogeneous Biological Systems. *Nature Reviews Genetics* **10**(2), 122–133.