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Ontology-assisted approach for learning causal Bayesian network structure

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To my family

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Abstract

Learning Bayesian network structure has been an active topic since they were introduced, especially when considering their causal interpretation. There have been several attempts at guiding the learning process by providing additional knowledge, usually supplied by experts. In the recent years, ontologies have gained popularity in terms of publishing domain knowledge in a formal, systematic and, above all, machine understandable way. It was to be expected for approaches to be developed that combine these two models for representing knowledge, made even more obvious when considering their underlying similarity.

In this work we will consider using the knowledge present in publicly available ontologies, focusing on causal knowledge, and using it to assist the construction of causal Bayesian networks. We will consider the needed assumptions to make the process sound and propose a structure learning algorithm. After an in-depth analysis of the algorithm we will consider its performance on a real-world dataset and compare it to existing approaches.

We have taken an example from the field of molecular biology because of the amount of datasets available, the high quality publicly available ontologies as the Gene Ontology, and the interest in using Bayesian networks for modeling gene interaction networks.

It will be shown that the devised approach is valid one and has many potential directions for future extension.

Sommario

L'apprendimento della struttura di reti Bayesiane è stato un argomento attivo da quando esse sono state introdotte, soprattutto se si considera la loro interpretazione causale. Ci sono stati diversi tentativi di dirigere il processo di apprendimento fornendo ulteriori conoscenze, di solito fornite da esperti. Negli ultimi anni, le ontologie hanno guadagnato popolarità in termini di pubblicazione di conoscenza del dominio in modo formale, sistematico e, soprattutto, utilizzabile da programmi informatici. Era da aspettarsi che vari approcci che combinano questi due modelli per la rappresentazione della conoscenza sarebbero stati sviluppati, e il tutto appare ancora più evidente se si considera la loro somiglianza di fondo.

In questo lavoro considereremo l'utilizzo della conoscenza presente in ontologie disponibili pubblicamente, concentrandoci particolarmente alla conoscenza causale, e usandola per assistere la costruzione di reti Bayesiane causali. Saranno prese in considerazione le ipotesi necessarie per rendere il processo coerente e in seguito proporremo un algoritmo per l'apprendimento di tali strutture. Dopo l'analisi approfondita dell'algoritmo vedremo le sue prestazioni su un set di dati preso dal mondo reale e confrontarlo con approcci esistenti.

Abbiamo preso un esempio dal settore della bioinformatica a causa della quantità di set di dati a disposizione, la disponibilità di ontologie pubbliche di alta qualità come la Gene Ontology, e l'interesse elevato per l'utilizzo di reti Bayesiane per la modellazione di reti di interazioni geniche.

Sarà mostrato che l'approccio messo a punto è valido e offre varie direzioni da considerare per una futura estensione.

1 Introduction

1.1 Motivation

The popularity of Bayesian networks for representing uncertain knowledge, and ontologies for storing machine readable and structured knowledge has made people consider combined approaches. The main motivation to consider such an approach is made obvious when realizing the high similarity of their underlying structures. This similarity allows for knowledge to be transferred both ways, and thus two main approaches have been considered. One line of thought tries to incorporate uncertainty into ontologies, while the other wants to exploit the knowledge present in them to guide the construction of the Bayesian network structure. Our approach will follow the latter one. Moreover, we will consider our Bayesian network to have a causal interpretation and will be interested solely in its structure, disregarding the form of the causal relations.

General interest in the causal interpretation of the Bayesian networks is due to the stability of its relations. Once we know there exist a causal relation between two variables we know it to be an objective and physical constraint in our world. This comes at a price, the task of finding and justifying such a relation has proven to be quite non-trivial, especially when the goal is to learn them from offline data. In that case, even under reasonable assumptions, which may not hold in general, the process is driven by covariation and does not give us the guarantee of causality.

On the other hand we can expect ontologies to comprise in themselves among others, also causal knowledge. This is exactly the knowledge we want to exploit and for which we believe that reflects the true state of the world for the give domain.

Following the discussion above, we can formulate the main idea behind our approach. We will be considering using publicly available domain knowledge in form of ontologies to assist the learning process of causal network structures. We say “assist” because the approach is based around a standard structure learning algorithm which uses the ontology for tuning up its results. This general outline of the approach leaves enough space for considering different points of interaction between the ontology knowledge and the structure learning algorithm.

1.2 Outline

This work is structured as follows. In section 2 we will start by introducing Bayesian networks, their causal interpretation and looking at both the general idea of structure learning and at real approaches and their building blocks. Next, in the same section, we will introduce the concept of ontologies and look at how can they be used for learning causal network structures. We will continue by looking at the reasoning process for inferring implicit knowledge present in the ontology, and focusing on the one needed for our application. Before venturing into a deeper analysis of our approach, in section 3, we will take a look at some similar approaches taken by various groups. Later, in section 4, we will deal with the analysis of our approach with a detailed consideration of each algorithm step and end by considering its computational complexity. In section 5, we will look at the performance of our approach on a real world example from the molecular biology domain, compare it to other approaches and discuss the results. To conclude, in section 6, we are going to consider the open issues and possible extensions of this work.

2 Background

2.1 Bayesian networks

2.1.1 Introduction

Bayesian networks, also called belief networks, probabilistic networks, or causal networks, were developed to facilitate the task of prediction and abduction[1] in artificial intelligence systems. In these tasks, it is necessary to find a coherent interpretation of incoming observations that is consistent with both the observations and the prior information at hand. Mathematically, the task boils down to the computation of $P(Y|X)$, where X is a set of observations and Y is a set of variables that are deemed important for prediction or diagnosis. The computation involves a straightforward application of the Bayes' rule [39].

Formally, Bayesian networks are directed acyclic graphs (DAGs) composed of nodes, which correspond to random variables, and directed edges between nodes, which indicate a direct influence of the source (parent) node to the target (child) node.

The set of nodes V and the set of edges E together define the *structure* of the Bayesian network $< V, E >$. The structure of the network specifies the *conditional independence* relationships that hold in the domain being modeled. Thus, inference over a large number of variables can be decomposed into a set of local calculations involving a small number of variables. Where conditional independence is defined as follows: given variables or sets of variables X, Y and Z we say that X and Y are conditionally independent given Z if

$$P(X, Y|Z) = P(X|Z)P(Y|Z), \tag{1}$$

which can be also written as

$$P(X|Y, Z) = P(X|Z). \tag{2}$$

Along with the structure, to fully specify a Bayesian network we need to know the conditionally probability distributions $P(X_i|Parents(X_i))$ for each random variable X_i, which

[1] Abduction is a form of logical inference that goes from observation to a hypothesis that accounts for the reliable data (observation) and seeks to explain relevant evidence.

are the *parameters* of the model. Whereas the structure defines the parents for each variable X_i the parameters define the degree of influence in a quantitative way.

Variables can be either discrete or continuous[2]. In the case of *discrete* variables for each variable X_i and its parents $Y_1, \dots, Y_k$ we can represent its distribution as a *conditional probability table* (CPT). If we take $n_1, \dots, n_k$ to be the number of possible values of variables $Y_1, \dots, Y_k$ respectively, the CPT for variable X_i will have $\prod_{i=1}^{k} n_i$ entries. This representation can describe any discrete conditional distribution, but having the downside that the number of free parameters is exponential in the number of parents.

For continuous variables, unlike the case of discrete variables, there is no representation that can represent all possible densities. A natural choice for multivariate continuous distributions is to use Gaussian distributions in the form of *linear Gaussian conditional densities*, according to which the conditional density for X_i given its parents is:

$$P(X_i|u_1, \dots, u_k) \sim N\left(a_0 + \sum_j a_j * u_j\, , \sigma^2\right). \qquad (3)$$

Thus, X_i is normally distributed around a mean that depends linearly on the values of its parents, and a variance independent of the parents' values. If all the variables have a linear Gaussian distribution the joint distribution is a multivariate Gaussian [16].

Markov equivalence

The notion of *Markov equivalence* will be needed once we start talking about structure learning algorithms, for which we will need the notion of *equivalence classes*.

When considering conditional independences, represented in the network structure by means of directed edges, we are not interested in the edge orientation. The graphs $X \rightarrow Y$ and $X \leftarrow Y$ both imply the same set of conditional independencies. Therefore, more than one graph can imply the exact same set of independencies even though their structures differ in the

[2] In this work only networks having all variables of the same kind will be considered.

orientation of some edges. We say for such graphs to be *Markov equivalent* and the set of all equivalent graphs forms an *equivalence class*. The Markov equivalence is formally defined in the following theorem.

Theorem: *Two DAGs are Markov equivalent if and only if they have the same underlying undirected graph and the same v-structures (i.e., converging directed edges into the same nodes, such that $a \rightarrow b \leftarrow c$, and there is no edge between a and c).* [16]

An equivalence class can be uniquely represented by a *partially directed acyclic graph* (PDAG), where a directed edge means that all the graphs in the class contain it. On the other hand an undirected edge denotes that graphs in the class disagree on its directionality.

d-separation

We are going to introduce the concept of *d-separation* since we are going to need it in a later section, when considering the structure learning algorithm. The intuition behind the concept is simple and can best be recognized if we attribute causal meaning to the arrows in the graph. In causal chains $X \rightarrow Z \rightarrow Y$ and causal forks $X \leftarrow Z \rightarrow Y$, the X and Y variables are marginally independent but become dependent once we condition on the Z variable. Figuratively, conditioning on Z appears to "block" the flow of information along the path, since learning about X has no effect on the probability of Y given Z.

Inverted forks $X \rightarrow Z \leftarrow Y$, representing two causes having a common effect, act the opposite way; if the X and Y variables are marginally independent, they will become dependent once we condition on the Z variable or any of its descendants.

Formally, we write:

Definition: *A path p is said to be d-separated (or blocked) by a set of nodes S if and only if:*

1. *p contains a chain $x \rightarrow z \rightarrow y$ or a fork $x \leftarrow z \rightarrow y$ such that the middle node z is in S or,*
2. *p contains an inverted fork (or collider) $x \rightarrow z \leftarrow y$ such that the middle node z is not in S and such that no descendant of z is in S.*

A set S is said to d-separate X from Y if and only if S blocks every path from a node in X to a node in Y.

2.1.2 Causality

A long tradition in psychology and philosophy has investigated the principles of causal understanding. We understand causation to be a relation between events in which the presence of some events causes the presence of others [20]. We assume causation to be a causal binary relation with the properties of being transitive, irreflexive, and asymmetric. That is:

1. if *A* is a cause of *B* and *B* is a cause of *C*, then *A* is also a cause of *C*,
2. an event *A* cannot cause itself, and
3. if *A* is a cause of *B* then *B* is not a cause of *A*.

Relative to the set of events causation can be direct or indirect. When we have two events of which one is the immediate cause of the other we say causation is direct. On the other hand when there is a chain of causally connected events for which *A* is the immediate cause and *C* the immediate effect then *A* and *C* are said to be in an indirect causal relationship. In such a relationship once it is known that an event has happened it *screens off* the events that are its direct and indirect causes from its direct and indirect effects to which we refer as the *causal Markov assumption*. By means of causal relationships we can construct a *causal network* representing some causal process in the world [39].

If willing to accept the causal Markov assumption we can interpret causal networks as Bayesian networks which are usually regarded as causal Bayesian networks (CBNs). When the assumption holds, the causal network satisfies the Markov independencies of the corresponding Bayesian network. One of the main differences between them is a stricter interpretation on the meaning of edges for the causal network: direct causal relationships, with parent nodes being causes, and child nodes effects. There is also a different interpretation of the conditional distributions which get interpreted as functional relationships between variables.

Moving from a probabilistic model to a causal one we get a model that is much more informative. While the joint distribution tells us how probable events are and how probabilities with subsequent observations change, a causal model also tells us how these probabilities would change as a result of external *interventions*. By means of interventions it is possible to test whether variable X causally influences variable Y. To do so we compute the marginal distribution of Y under the action $do(X = x)$, namely $P_x(y)$[3], for all values x of X and test whether that distribution is sensitive to x. This understanding of causal influence permits us to see precisely why, and in what way, causal relationships are more "stable" than probabilistic ones. The stability comes from the fact that causal relationships are *ontological*, describing objective, physical constraints in our world, whereas probabilistic relationships are *epistemic*, reflecting what we know or believe about the world. Therefore, causal relationships should remain unaltered as long as the environment remains unchanged. We can see this in the following example [39].

The simple Bayesian network shown in Figure 1 describes relationships among the season of the year, whether rain falls, whether the sprinkler is on, whether the pavement would get wet, and whether the pavement would be slippery. All the variables are discrete; *season* having four values, while all the others are binary. Now let us consider two relationships:

1. a causal one, "Turning the sprinkler on would not affect the rain",
2. and the probabilistic counterpart, "The state of the sprinkler is independent of the state of the rain".

By looking at Figure 1 we can see two ways in which the second relationship would change while the first one would remain unaffected. Firstly *rain* and *sprinkler* are conditionally independent only when *season* is known[4], which makes the relationship 2) change from false to true. The same relationship changes from true to false once the variable *wet* is observed through the *explaining away* effect. On the other hand relationship 1) remains true regardless of what observations we make on the other variables. In fact it will remain invariant to changes

[3] $P_x(y)$ denotes the distribution resulting from the intervention $do(X = x)$ that sets a subset X of variables to constants x.

[4] $P(sprinkler \mid season \wedge rain) = P(sprinkler \mid season) \equiv sprinkler \perp\!\!\!\perp rain \mid season$ – if we observe that is raining there is a greater probability the season is a rainy one which in turn makes it less likely for the sprinkler to be on.

in all mechanisms shown in this causal graph and therefore we can see it exhibits greater robustness [39].

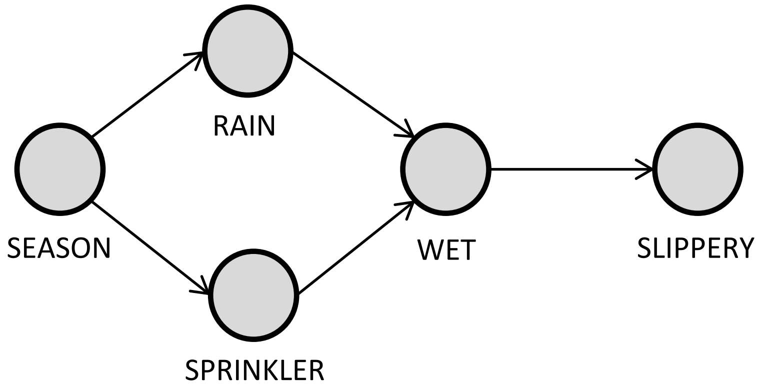


Figure 1 – A simple causal network

Another consideration we should make is that it is understood that independence assumption carried by the DAG does not necessarily imply causation. On the other hand the stability of causal relationships mentioned above is the reason for the ubiquity of DAG models in AI applications. Therefore, probabilistic relationships may be helpful in hypothesizing initial causal structures from uncontrolled observations, but once the acquired knowledge is cast in causal structures the probabilistic interpretation tends to be forgotten.

2.1.3 Causal structure learning

Looking at the world as consisting of a collection of causal systems and each system consisting of a set of observable *causal variables* we can translate such systems into causal Bayesian networks. To learn such a network we observe causal systems on a set of trials on which each variable takes a specific value [20]. For example an autonomous intelligent system attempting to build a workable model of its environment cannot rely exclusively on preprogrammed causal knowledge; rather, it must be able to translate direct observations made using its sensors to cause-and-effect relationships [39].

The problem lies in the fact that data thus collected comprises a set of passive observations on which we can perform statistical analysis driven by covariation instead of causation. Learning causal relationships from raw data has been on philosophers' wish list since the 18th century. The approach taken to achieve this goal has been to try understanding the process by which humans acquire causal relationships and trying to build a computational model based on it [39].

Human inference of causal relationships is taken to rely primarily on universal cues such as spatiotemporal contingency or reliable covariation between effects and their causes as well as on domain-specific knowledge [33]. Accordingly, most theories of causation invoke an explicit requirement that a cause precedes its effect in time. Yet temporal information alone cannot distinguish genuine causation from spurious associations caused by unknown factors – the barometer falls before it rains yet it does not cause the rain [39]. Humans also heavily reside on the possibility of repeatedly performing interventions to discover causal laws.

In order to learn the structure of a causal network from raw data we need to make some assumptions. First, we assume that causal networks can provide reasonable models of the domain. Sometimes a stronger version of this assumption is required, namely that causal networks provide a perfect description of the domain. The second assumption states that there are no *latent* or hidden variables that affect the observable variables [37]. This assumption does not hold in all domains and we will see that it does not hold in the domain of molecular biology when dealing with microarray experiments.

From the above assumptions it follows that one of the possible structures over the domain variables is the “true” causal network. However, from observations alone it is not possible to distinguish between causal networks that belong to the same equivalence class. In consequence four different approaches have been developed: *constraint-based learning*, *score-based learning, Bayesian model averaging* and *hybrid approaches*.

Constraint-based learning methods view a Bayesian network as a representation of independencies. They try to test for conditional dependence and independence in the data in order to find a network, or more precisely an equivalence class of networks, that best explains them. Constraint-based methods are quite intuitive. They decouple the problem of finding structure from the notion of independence. They also follow more closely the definition of Bayesian networks: we have a distribution that satisfies a set of independencies, and our goal is to find the equivalence class for this distribution [55]. Unfortunately, these methods can be sensitive to failures in individual independence tests. It suffices that one of these tests return a wrong answer to mislead the network construction procedure [45].

Score-based methods, also known as search-based, view Bayesian networks as specifying statistical models and address learning as a model selection problem. All of them operate on the same principle: we define a hypothesis space of potential models — the set of possible network structures we are willing to consider — and a scoring function that measures how well the model fits the observed data. Our computational task is then to find the highest-scoring network structure. The space of Bayesian networks is a combinatorial space, consisting of a super-exponential number of structures — $2^{O(n^2)}$. Therefore, the problem translates to optimization problem. There are very special cases where we can find the optimal network. In general, however, the problem is (as usual) NP-hard, and we resort to heuristic search techniques. Score-based methods consider the whole structure at once; they are therefore less sensitive to individual failures and better at making compromises between the extent to which variables are dependent in the data and the "cost" of adding the edge. The disadvantage of the score-based approaches is that they pose a search problem that may not have an elegant and efficient solution [55].

Hybrid approaches combine the two learning methods described above, and are sometimes called *search-and-score-based methods* [55].

Finally, instead of attempting to learn a single structure the Bayesian model averaging methods generate an ensemble of possible structures. These methods extend the Bayesian reasoning and try to average the prediction of all possible structures. Since the number of structures is immense, performing this task seems impossible. Yet, for some classes of models this can be done efficiently, and for others we need to resort to approximations [31].

2.1.4 State of the art algorithms

Here we will take a look at the various algorithms devised for learning causal Bayesian network structures. Since there are many such algorithms differing only in the details, such as the measure employed for network scoring, only an overview will be presented.

2.1.4.1 Score-based methods

Let us start with the scoring-based algorithms. Their main difference is the metric used for scoring the network which is employed by all algorithms except when performing an *exhaustive search*[5]. The metrics differ in the assumptions they require, e.g. the type of data (discrete or continuous). Some of the metrics used are listed below.

Maximum likelihood - measures the strength of the dependencies between variables and their parents. In other words, it prefers networks where the parents of each variable are informative about it. The maximum likelihood network will exhibit a conditional independence only when that independence happens to hold exactly in the empirical distribution. Due to statistical noise, exact independence almost never occurs, and therefore, in almost all cases, the maximum likelihood network will be a fully connected one. In other words, the likelihood score overfits the training data. [6, 31]

Bayesian information criterion (BIC) - the score exhibits a trade-of between fit to data and model complexity: the stronger the dependence of a variable on its parents, the higher the score; the more complex the network, the lower the score [6, 43].

Akaike information criterion (AIC) – can be generally used for the identification of an optimum model in a class of competing models. It is a measure of the lack-of-fit of the chosen model and the increased unreliability of the chosen model due to the increased number of model parameters. The best approximating model is the one which achieves the minimum AIC in the class of the competing models [6, 42].

Bayesian metric with Dirichlet priors and equivalence (BDe) - evolved from the search for a network with the largest posterior probability, given priors over network structures and parameters. It is based on the concept of sets of likelihood equivalent network structures, where all members in a set of equivalent networks are given the same score. Used only with discrete data [6, 51].

[5] Because of the triviality and practical infeasibility for networks with more than a small number of variables it won't be included in the list.

Bayesian metric with Gaussian priors and equivalence (BGe) – BDe counterpart for continuous data [31].

Mutual information tests (MIT) - measures the degree of interaction between each variable and its parents. This measure is, however, penalized by a term related to the Pearson X^2 test of independence. This term attempts to re-scale the mutual information values in order to prevent them from systematically increasing with the number of variables [6].

When we fix the scoring metric we still need to decide the rules that will drive the searching process. The rules describe changes made to the structure at each step of the algorithm. They can be made either on a local scale (atomic) such that only one edge gets added, removed or changes the directionality, or on a larger scale (global) when the structure can change substantially [37].

The simplest and most commonly used is the greedy algorithm, which at each step looks for the change in the structure with the best score. This procedure suffers from the fact it has a high probability of poor performance because of ending up in a local minima/maxima. On the other hand, more complex solutions, such as using metaheuristics (Hill-Climbing, Genetic algorithm, Tabu search, Simulated annealing,…) still offer no guarantee of finding the best solution but are less likely to get stuck with a low fitting structure [24].

2.1.4.2 Constraint-based methods

We continue by considering some of the constraint-based methods. Unlike the score-based methods which always return a fully oriented Bayesian network or a set of networks, these methods in general will return only an equivalence class, usually in the form of a single PDAG. The learning process is for most algorithms performed in two phases. In the first phase the algorithm looks for (in)dependencies using one of the possible independency tests and outputs the network skeleton[6]. The second phase tries to orient as many edges by following a set of rules [1, 2, 4, 9, 31, 32, 39, 45].

[6] The skeleton of a DAG is a graph having the same nodes and edges, but all edges being undirected.

The commonly used algorithms are *IC (inductive causation)*[39, 45], *SGS (Spirtes, Glymour and Scheines)* [39, 45], *PC (Peter and Clark)* [39, 45], *Incremental Association Markov Blanket (IAMB or IA)* [49], *TPDA (Three Phase Dependency Analysis)* [8] and *RAI (recursive autonomy identification)* [52]. Their short descriptions are given below.

IC – the algorithm starts with the empty graph[7] and for each pair of variables X and Y searches for a subset of nodes S_{XY}[8] such that they are conditionally independent given S_{XY}. If no such subset exists it adds an undirected edge between X and Y. Once the undirected graph has been constructed it orients the edges. First it looks for all nonadjacent pairs of variables X and Y that have a common neighbor Z and checks if S_{XY} contains Z. If that is not the case then it orients the edges to get the v-structure $X \rightarrow Z \leftarrow Y$. It ends by trying to orient as many undirected edges as possible such that any alternative orientation would yield a new v-structure or a directed cycle.

SGS – same as the IC algorithm except it starts with a fully connected graph and proceeds by removing edge by edge.

PC – based on the previous two algorithms. It starts with a fully connected graph and continues with a systematic search for the sets S_{XY}. First it starts with S_{XY} of cardinality zero, then cardinality 1, and so on; meanwhile edges are removed from a complete graph as soon as separation is found. This refinement enjoys polynomial time complexity in graphs of finite degree, because at every stage the search for a separating set can be limited to nodes that are adjacent to the two taken into consideration for independence. The simplicity and efficiency of this algorithm are the reasons for choosing it to be the base algorithm for our solution and therefore it will be discussed in greater length later on.

IA - consists of two phases, a forward and a backward one. An estimate of the Markov blanket for a variable X, denoted as $MB(X)$, is kept in the set CMB. In the forward phase all variables that belong in $MB(X)$ and possibly more (false positives) enter CMB while in the backward phase the false positives are identified and removed so that $CMB = MB(X)$ in the

[7] Graph containing all the nodes but no edges between them.
[8] A subset of nodes that does not contain X and Y.

end. The heuristic used in IA to identify potential Markov blanket members in the first phase is the following: start with an empty candidate set for the CMB, and admit into it (in the next iteration) the variable that maximizes a heuristic function $f(Y \,;\, X \mid CMB)$. Function f should return a non-zero value for every variable that is a member of the Markov Blanket for the algorithm to be sound, and typically it is a measure of association between X and Y given CMB. In backward conditioning, the second phase, we remove one-by-one the features that do not belong to the $MB(X)$ by testing whether a feature Y from CMB is independent of X given the remaining CMB.

TPDA – as the name states the algorithm has three phases: drafting, thickening and thinning. In the first phase the algorithm computes mutual information for each pair of nodes as a measure of closeness, and creates a draft based on this information. The draft is a singly connected graph (a graph without loops). In the second phase, the algorithm adds edges to the current graph when the pairs of nodes cannot be separated using a group of CI tests. The result of the second phase contains all the edges of the underlying dependency model given that the underlying model is *monotone DAG-faithful*[9]. In the third phase, each edge is examined using a group of CI tests and it will be removed if the two nodes of the edge are conditionally independent. The result of this phase contains exactly the same edges as those in the underlying model when the model is monotone DAG-faithful. At the end of this phase, the algorithm also carries out a procedure to orient the edges of the learned graph. This procedure may not be able to orient all the edges. The complexity of this algorithm is $O(n^4)$. It has been shown that the monotone DAG-faithfulness assumption together with the faithfulness assumption restricts the class of possible Bayesian network structures to ones for which the optimal solution can be found in $O(n^2)$.

RAI - starting from a complete undirected graph and proceeding from low to high cardinality of separation sets, the RAI algorithm uncovers the correct pattern of a structure by performing the following sequence of operations: test of CI between nodes, followed by the

[9] The assumption states that the (conditional) mutual information between a pair of variables is a monotonic function of the set of active paths between those variables. The more active paths between the variables the higher the mutual information.

removal of edges related to independences, edge orientation according to rules (same ones as in the IC algorithm), and graph decomposition into autonomous sub-structures. For each autonomous sub-structure, the RAI algorithm is applied recursively, while increasing the order of CI testing. While we have already seen the first two steps in other algorithms we will take a closer look at the last one. Decomposition into separated, smaller, autonomous sub-structures reveals the structure hierarchy. Decomposition also decreases the number and length of paths between nodes that are CI-tested, thereby diminishing, respectively, the number of CI tests and the sizes of condition sets used in these tests. Both reduce computational complexity. Moreover, due to decomposition, additional edges can be directed, which reduces the complexity of CI testing of the subsequent iterations. Following decomposition, the RAI algorithm identifies ancestor and descendant sub-structures; the former are autonomous, and the latter are autonomous given nodes of the former.

After looking at the description of the constraint-based algorithms we see that each resides on testing for conditional independence. In principle, each could use any of the tests that will be mentioned shortly. The tests differ in the data they can be applied to, either discrete or continuous, but all of them test only for linear dependencies. It has been argued that datasets in different domains are known to have a high number of non-linear dependencies between the variables making the use of this test inappropriate [27]. The most commonly used tests are: *Pearson's chi-squared test*, *Fisher's Z test* and *mutual information*. [45]

Mutual information - measures the information that X and Y share. It measures how much knowing one of these variables reduces uncertainty about the other. For example, if X and Y are independent, then knowing X does not give any information about Y and vice versa, so their mutual information is zero. At the other extreme, if X and Y are identical then all information conveyed by X is shared with Y. That is, knowing X determines the value of Y and vice versa. It can be used with both continuous and discrete data. The estimation is sometimes improved through combination with other information by making it closer to the value of the provided information, and by doing so we get the *shrinkage estimator of mutual information*. To calculate the mutual information we use formulas (4) and (5) for discrete and continuous case respectively [58].

$$I(X;Y) = \sum_{y \in Y} \sum_{x \in X} p(x,y) \log\left(\frac{p(x,y)}{p(x)p(y)}\right) \tag{4}$$

$$I(X;Y) = \int_Y \int_X p(x,y) \log\left(\frac{p(x,y)}{p(x)p(y)}\right) dx\, dy \tag{5}$$

Pearson’s chi-squared test (X^2) - tests a null hypothesis, the one stating that the frequency distribution of certain events observed in a sample is consistent with a particular theoretical distribution. The events considered must be mutually exclusive and have total probability of one. A common case for this is where each event covers an outcome of a categorical variable. Therefore, it can be used only for discrete datasets. When testing independence of variables we use the following formula:

$$X^2 = \sum_{i=1}^{r} \sum_{j=1}^{c} \frac{\left(O_{i,j} - E_{i,j}\right)^2}{E_{i,j}} \tag{6}$$

$$E_{i,j} = \frac{\left(\sum_{n_c=1}^{c} O_{i,n_c}\right) \cdot \left(\sum_{n_r=1}^{r} O_{i,n_r}\right)}{N} \tag{7}$$

where r and c are the number of rows and columns respectively, N is the total sample size, and $O_{i,j}$ is the observed frequency count at level i of the first and at level j of the second variable. A chi-squared static larger than the critical point (0.05) is commonly interpreted by applied workers as justification for rejecting the null hypothesis, stating the variables are independent [60].

Fisher’s Z test – is used when dealing with continuous Gaussian random variables. After performing Fisher's z-transformation of the partial correlation, the test statistic has value

$$\sqrt{N - |\boldsymbol{Z}| - 3} \cdot |z(\hat{\rho}_{XY \cdot \boldsymbol{Z}})| \tag{8}$$

where the z transformation is defined as

$$z(\hat{\rho}_{XY\cdot\boldsymbol{Z}}) = \frac{1}{2}\ln\left(\frac{1+\hat{\rho}_{XY\cdot\boldsymbol{Z}}}{1-\hat{\rho}_{XY\cdot\boldsymbol{Z}}}\right) \tag{9}$$

and the recursive form of the partial correlation as

$$\hat{\rho}_{XY\cdot\boldsymbol{Z}} = \frac{\hat{\rho}_{XY\cdot\boldsymbol{Z}\setminus\{Z_0\}} - \hat{\rho}_{XZ_0\cdot\boldsymbol{Z}\setminus\{Z_0\}}\hat{\rho}_{Z_0Y\cdot\boldsymbol{Z}\setminus\{Z_0\}}}{\sqrt{1-\hat{\rho}^2{}_{XZ_0\cdot\boldsymbol{Z}\setminus\{Z_0\}}}\sqrt{1-\hat{\rho}^2{}_{Z_0Y\cdot\boldsymbol{Z}\setminus\{Z_0\}}}}, \forall\, Z_0 \in \boldsymbol{Z}. \tag{10}$$

The terms in the above formulas are: N – the sample size; $\boldsymbol{Z}$ – separation set; X, Y – variables being tested for independence given $\boldsymbol{Z}$. In a multivariate normal distribution, zero partial correlation is equivalent to conditional independence therefore the null hypothesis is

$$H_0: \hat{\rho}_{XY\cdot\boldsymbol{Z}} = 0. \tag{11}$$

The test statistic is (asymptotically for large enough N) standard normally distributed. We reject the null hypothesis with confidence α if the test statistic is greater than

$$\Phi^{-1}\left(1-\frac{\alpha}{2}\right) \tag{12}$$

where $\Phi(\cdot)$ is the cumulative distribution function[10] of a Gaussian distribution with zero mean and unit standard deviation [57, 59].

[10] It describes the probability that a real-valued random variable X with a given probability distribution will be found at a value less than or equal to x. In the case of a continuous distribution, it gives the area under the probability density function from minus infinity to x.

2.2 Ontology

2.2.1 Introduction

Over the last few years ontologies have emerged as means of providing a formal and structured representation of knowledge which can range from generic real world knowledge to strictly domain-specific (e.g., linguistics, semantic web, biology, etc.). They represent not only a fixed structure but also the basis for deductive reasoning [14]. The purpose of employing an ontological representation is to capture concepts in a given domain in order to provide a shared common understanding of this domain, enabling interoperability and knowledge reuse but also machine-readability and reasoning about information through inference. They are deterministic in nature, consisting of concepts and facts about a domain and their relationships to each other. The most common definition of an ontology is that it is a formal, explicit specification of a shared conceptualization. That is, an ontology is a description (like a formal specification of a program) of the concepts and relationships that can exist for an agent or a community of agents. It provides a shared vocabulary, which can be used to model a domain, the type of objects and/or concepts that exist, and their properties and relations [13, 14, 28, 29, 34].

The questions we are interested about ontologies are: what are ontologies for, and how can they be used in the domain of learning Bayesian network structures. To answer the first question is fairly easy – the purpose of ontologies is to enable knowledge sharing and reuse. The second question does not have a trivial and surely not a single answer. We will see some devised approaches in the section "Related works", but for now we'll just argue that bringing additional knowledge could undoubtedly be useful to guide the structure learning process. We saw that causality cannot be inferred from data alone, thus we will seek help from the additional information about variables and their relationship in the real world, in form of ontologies.

2.2.2 Causal relationships

Except for "is a", which is implied by the subclass statements, relationships in ontologies are user defined and domain specific (e.g. "father of", "teaches", "synonymy", etc.). Relationships that we are interested in are those that could imply some kind of causal relationship between the ontology terms, which could be in turn directly translated into directed edges of a causal Bayesian network.

We will take a closer look by introducing a simple example. The ontology presented in Figure 2 could be part of some larger disease ontology which deals with disease taxonomy, the relations of diseases and their symptoms, the location of the disease, etc. The larger ontology could also have other relationships as well as a more intricate taxonomy.

The relationships in this example are: “is_a”, “located_in”, and “has_symptom”. The “is_a” relationships, also called *subclass relationship,* is implicit and it follows from the class subsumption statements formally written as

$$Subclass \sqsubseteq Superclass \tag{13}$$

which we interpret as “Subclass is included in Superclass”, or alternatively and less formally “All the things from the world that are Subclass are also Superclass”. The relation is reflexive, antisymmetric and transitive[11]. From what we have seen earlier, it is clear that this relationship would not do as a causal one, which we know to have quite different properties than the ones listed for the “is_a” relation. The simple informal example of “Cause is_a Effect” would suffice to back up our intuition.

Next we will consider the user-defined “located_in” relationship. We can see that even though its properties are different from the “is_a” relationship it still does not have a causal meaning. The relation is irreflexive, asymmetric and transitive.

In the end there is the “has_symptom” relation, which is also user-defined and its properties differ from both previously mentioned relationships. It is irreflexive, asymmetric and transitive. These are the properties we want for a causal relationship in order to include it in our causal Bayesian networks. As we can see the “has_symptom” relation does imply causation. The disease is the cause for symptoms to arise. Therefore, when the ontology states that a disease has some symptoms it means that the symptoms are a consequence of (they are caused by) the

[11] Fromally defined in the appendix section 7.1.

disease. Of course, not all relationships that have these properties are causal relationships. For example, we can think of an ontology about humans and their customs, which has a relationship "bigger than". This relation does not have a causal interpretation because the statement - Elephant "bigger than" Bunny – does not imply that elephants are the causes of bunnies even though the relation is irreflexive, asymmetric and transitive.

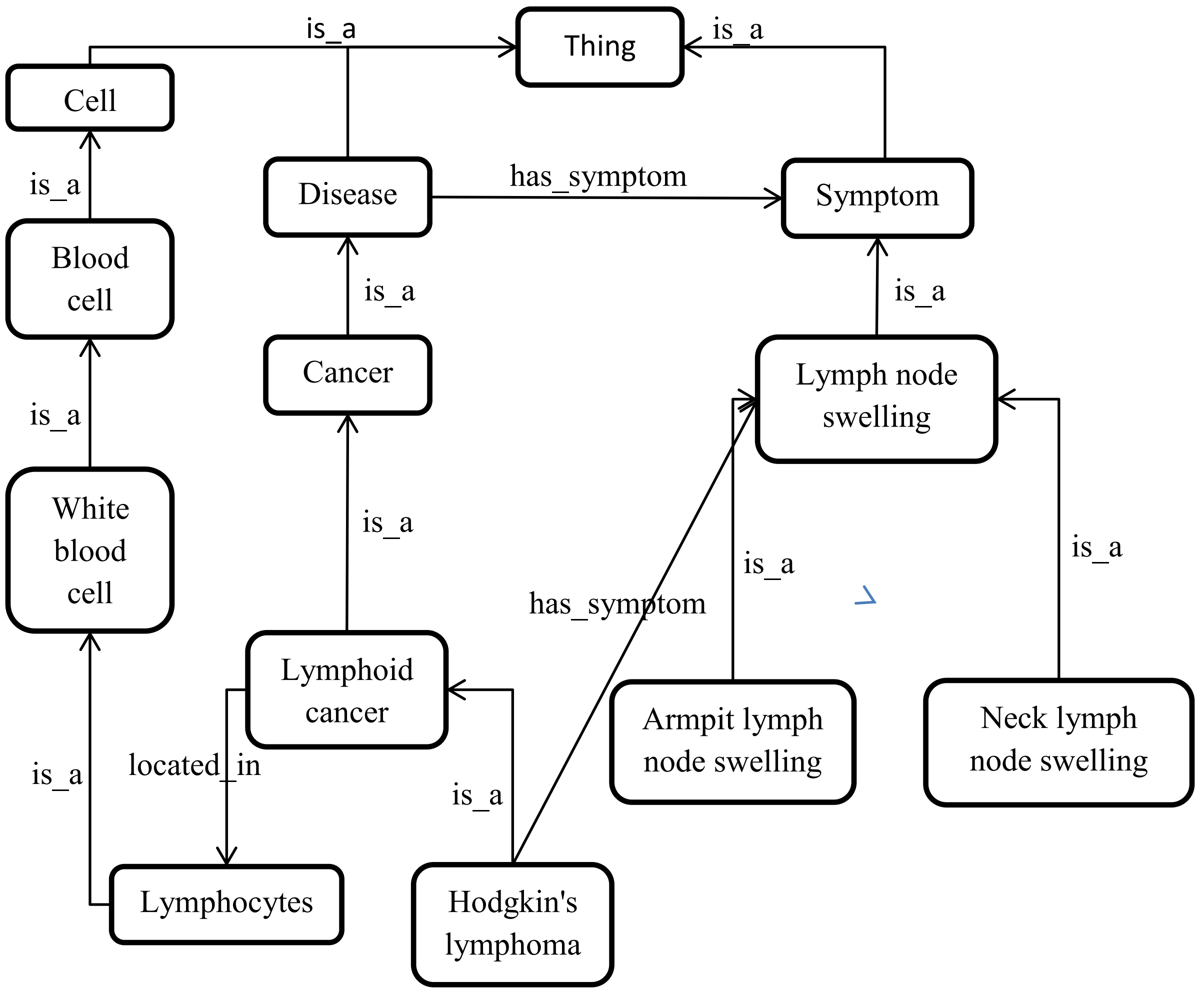


Figure 2 – An example ontology

In the discussion above we argued that some of the relationships can be regarded as causal. But in the ontology the relationships are not defined for each two terms for which the relationship holds but only for their most specific ancestors. This we can see in Figure 2 if we consider the relationship of the "Hodgkin's lymphoma" and "Neck lymph node swelling" nodes.

Their connection is not explicitly stated but it can be easily inferred since the latter is a "Lymph node swelling" which is in relation "has_symptom" with the "Hodgkin's lymphoma" node. Which tells us that the "is_a" and "has_symptom" relationship form chain rules that can be formalized as

$$\text{has\_symptom} \circ \text{is\_a} \sqsubseteq \text{has\_symptom}. \tag{14}$$

In order to infer if some relationship holds between to terms, either directly or indirectly, we will have to *reason* over the ontology by means of an inference engine usually referred to as a *reasoner.*

2.2.3 Reasoning

Reasoning is the process of inferring logical consequences from a set of explicitly asserted facts or axioms. The process is performed by a reasoner which typically provides automated support for reasoning tasks such as classification and querying. Reasoning is needed, as we have already seen in the previous example, because knowledge in an ontology might not be explicit and a reasoner is required to deduce implicit knowledge so that the correct query results are obtained.

For our needs we will need a reasoner to find out if there exists a causal relationship between ontology terms. Unfortunately, the available reasoners (FaCT++, HermiT, Pellet, etc.) do not provide built-in methods for performing such inference. Therefore, it was needed to think of a procedure that will rely on the available functionalities, mainly subclass and superclass retrieval.

Before we continue by showing the steps needed to perform the needed inference process, we will introduce some notation to make it more understandable. We have already seen subsumption statements which use the $\sqsubseteq$ operator and now we will introduce another class expression which deals with relations. It is the *qualified existential restriction* usually written as

$$\exists\, relation.class \tag{15}$$

and our procedure will heavily rely on it. It is nothing more than a complex class denoting the set of all objects of the universe that are in relation "relation" with the objects from "class". For example, $\exists\ parentOf.Female$ is the set of all objects that have female children.

Now we can specify the steps of the process for inferring the presence of a causal relationship between two terms that we will refer to as *Cause* and *Effect*.

1. Find the superclasses of *Effect*.
2. Find all the classes that have a causal relation to the classes retrieved in step 1.
3. Find if the set of the classes retrieved in steps 2 contains *Cause.*
4. If it does, there exists a causal relationship between *Cause* and *Effect*.

The explanation for the given procedure is the following. First in steps 1 and 2 we want to find all the classes that are causally related to the *Effect* class or any of its ancestors, since when a class is related to an ancestor, the relation also influences its descendant classes. If the *Cause* class is among the classes that are causally related to the *Effect* or some of its ancestors we can infer that there exists a causal relationship between the two.

It might be tempting to consider taking into account subsets of the *Effect* class or subsets/supersets of the *Cause* class, but we will show that such inference is not sound. When we consider the subsets of the *Effect* class it is clear that if we have a cause that causally influences a subset of the descendants this relation does not tell us anything about its relation to the *Effect* class. Each descendant has an additional chunk of information which might be the reason for the presence of the causal relation. Even if all the descendants would be causally related to the *Cause* class it would not be enough to justify the existence of the relation for the *Effect* class because there might be other subclasses not yet present in the ontology which are not causally related to the *Cause* class. The same kind of reasoning can be used when considering subclasses of the *Cause* class.

On the other hand if we consider including the superclasses of the *Cause* class when looking for its relation to the *Effect* class, two problems arise. The first one being the possibility that situations might arise in which a class is causally related to its own ancestor. The intuition behind it is that those relations are to general because they involve quite general terms. For example, in the *Biological processes* ontology cases as the following arise: the ancestor of the *Cause* term is “regulation of biological process” which is related to “biological process” through the “regulates” relation, but the *Cause* term is itself a “biological process” (which is also the *top class*[12] of the ontology). Such a relation tells us very little since it can be understood as a tautological statement. A more general rule would be to disregard relationships that are “too high” in the hierarchy. But it is not possible neither to state how high is too high nor to know during the reasoning process know where the terms reside since the ontologies are represented using DAG which does not have a fully defined ordering of terms.

The other problem that would arise if we were to consider *Cause* class superclasses is related to the previous one but is more sever. Let us consider four classes X, Y, W and Z, where Y and Z are subclasses of X and W respectively, moreover X and Y regulate W and Z respectively. Now, if we were to try inferring a causal relationship between Y and any sibling of Z by looking at both the causal relation of Y and X. If we were to consider superclasses of Y we would find a causal relation because of the relation existing between X and W. But such a conclusion is wrong because we know for a fact that Y causally influences only Z while the conclusion drawn would be that it is causally related not only Z’s ancestors but also to all its siblings.

The exact way the described process will be used is going to be described in subsequent sections. Now we will turn to look at some related works in which ontologies were used in the process of learning the Bayesian network structure.

[12] The top class of an ontology is its root node. That is, all the classes in the ontology are in descendants of the top class. See also footnote 17.

3 Related work

Here we will discuss some approaches taken to combine the knowledge present in ontologies and Bayesian networks. They are concerned with mapping the ontology structure to a Bayesian network or representing uncertain knowledge in ontologies. The main idea behind these approaches is exploiting the structure similarity between Bayesian networks and ontologies, namely the underlying DAG.

The first work was done by E. Helsper and L. van der Gaag [22] and it dealt with devising a knowledge-engineering methodology for constructing and maintaining Bayesian networks. Their approach makes use of a manually constructed ontology which gets translated into a BN. The ontology here is used to make it easier for experts to model the domain knowledge that will be needed in the BN. In this approach as it will also be the case in others, there is no existing ontology whose knowledge is being exploited but it is just a more human-readable representation of the knowledge that gets translated into a BN.

Later, an extension of the OWL language for ontologies was proposed by Z. Ding and Y. Peng [14] in order to incorporate probabilistic knowledge which would allow for simpler translation process that would in turn allow probabilistic reasoning over the constructed BN. Again, we have a mapping from the ontology to the BN structure with the additional information of probabilistic markups attaching probabilities to classes and relations which are used for constructing conditional probability tables. A later extension of his approach allowed for automatic ontology mapping between ontologies.

A. Devitt, B. Danev and K. Matusikova [13] continued on the idea from Helsper and van der Gaag to devise an algorithm for translating ontologies into Bayesian networks in the telecommunications domain. In this system, the ontology model has the dual function of knowledge repository and facilitator of automated workflows while the generated BN serves to monitor effects of management activity, forming part of a feedback loop for self-configuration decisions and tasks. All in all this work just puts in practice the previous idea and deals with the implementation issues more thoroughly.

In the medical domain Jeon and Ko [29] proposed a semi-automatic algorithm which extracted nodes from an ontology and let the expert draw the causal relationships between them. Such an approach only facilitates the BN construction by providing the expert with a user friendly interface.

For the same domain in a later paper Zheng, Kang and Kim [54] proposed another way for incorporating uncertainty in ontologies. Their approach had the goal of both adding uncertainties in an ontology and allowing for the probability distribution to be updated by adding new data. They did it by adding additional (probabilistic) information into the ontology and upon the presence of new data the BN gets extracted from the ontology and its CPTs get updated. This approach uses the benefits of both BNs and ontologies, each bringing its full functionality into the system.

Ishak, Leray and Amor [28] again deal with the translation of the ontology into the BN structure with the difference that they use objective oriented Bayesian networks (OOBN). The advantage of using OOBN is in the fact that nodes can be assigned properties and be represented in a hierarchy making them more similar to ontologies than regular BNs. It is straightforward to see that by means of the hierarchy it is possible to translate the ontologies' "is_a" relationship into the OOBN.

The last and closest approach to the one discussed in this work was proposed by Messaoud, Leray and Amor [34]. They use the knowledge and functionalities present in both models to transfer the knowledge both ways. First they use the knowledge present in the ontology to constrain the possible Bayesian network structures and guide the learning process. In a latter phase the BN structure is used to update the ontology structure by adding newly found causal relationships between terms. Unlike our approach they impose the following constraints:

- each causal graph node must be modeled by a corresponding concept in the domain ontology,
- and the causal relations have to be defined between all elements of the ontology for which it holds.

These constraints do not allow the usage of existing ontologies but only of those designed by experts, while in our work we would like to take advantage of preexisting ontologies. These ontologies are usually curated by experts and constantly evolving.

In the next section we are going to look at our solution which was inspired by ideas discussed in the aforementioned works.

4 The algorithm

The main goal of the proposed approach is learning the Bayesian network structure using a constraint-based algorithm and exploiting the knowledge present in the ontology to try orienting the remaining undirected edges. By using only the former will in most cases result in forming a PDAG structure. For this purpose we can use one of many algorithms mentioned in earlier sections. Which one depends on the characteristics of the data we are dealing with and most of all on the quality of results produced. In our case it will be a variant of the PC algorithm which uses continuous data. The knowledge present in the ontology can be used to infer connections between variables and it can be placed at different stages:

- before using the constraint-based algorithm in order to find connections in order to lower the number of possible structures,
- after using the constraint-based algorithm but before it assigns edge orientations[13],
- after the constraint-based algorithm has produced a PDAG structure to infer the orientation of undirected edges,
- and same as in the last case with the additional task of checking the correctness of the orientation of the directed edges.

Moreover, the ontology could be used in combination even with a score-based approach but we are not going to deal with it in this work.

Our approach tried to lesser the constraints imposed upon the format of the ontology in order to allow using popular existing ontologies from different fields such as biology, medicine, chemistry, and others. All the user has to define is the causal relationship that is present in the ontology such as "has_symptom" or "regulates" since each ontology contains different such relations.

One important question is how do we connect the BN variables to the concepts present in the ontology? The approaches we have seen in the previous section make either the user select the concepts to be used or just use all the leaf concepts. In our approach we take a

[13] Given the algorithm performs the processes of finding edges and orienting them in different stages.

somewhat different approach where we annotate the nodes of the BN with terms from the ontology. This was done by taking into consideration how genes in the bioinformatics field get annotated with ontology terms. Each gene can have different functions and be part of different pathways. Therefore, a single annotation is not enough. In the same way we annotate our variables in the BN with terms of the given ontology. This way we are not bound to having an ontology with all the variables present in the BN and we can also transfer more information to the BN. On the other hand we need to provide a mapping between the BN variables and the ontology terms. Such mappings already exist in some domains, for example in bioinformatics between genes and terms from the Gene Ontology.

4.1 Steps of the algorithm

We have seen all the needed components for our algorithm and now we can specify its steps and afterwards go through them in detail. As we mentioned earlier the ontology can be used at different points of the algorithm but in this work only one will be considered leaving the other options for future work. The algorithm will go through the following steps:

1. Data preparation
2. Structure learning with PC algorithm
    a. Independence testing
    b. Edge orientation
3. Node annotation
4. Inferring undirected edge orientation from the ontology

4.1.1 Data preparation

This step is strictly speaking not part of the algorithm but is crucial and the result highly depends on it. For the purposes of our algorithm it won't be needed to discretize the data however it is required to be in a proper format and missing values have to be taken care of. The downside of this approach is not having the possibility to deal with categorical variables for which a different version of the PC algorithm or a different algorithm altogether should be used.

Since the formatting part of the data preparation step involved only parsing of the dataset we are not going look into it. However, dealing with missing values requires some attention. Datasets containing experimental data usually contain a fair amount of missing values especially in high-throughput methods such as microarray experiments. To sanitize such a dataset a couple of methods have been devised which try to impute the missing value with a value similar to values of that the variable in other experiments. One such method which was used in our work is the *kNNimpute* algorithm [48].

The kNNimpute algorithm works as follows. If a variable misses the value for the first experiment, the algorithm will go looking for k other variables that have similar values in other experiments. In the end it will assign the value that is calculated as a weighted average of the k nearest variable values in the first experiment. The algorithm can be used with different metrics for calculating the distance. In our case the distance metric used was the Euclidian one. It has been shown empirically that using this metric gives the best results [48].

The only parameter that influences the output of the kNNimpute algorithm is the minimum percentage of data values present for a variable over the experiments. This threshold was set to a quite low value (10%) in order to retain as many variables as possible. By doing so we have lessened the importance of having a dataset that faithfully resembles the real data, and are more concerned with having as much data as possible.

4.1.2 Structure learning with PC algorithm

We have already given some overview of this algorithm in an earlier section. Now we will give a closer look at the details regarding its implementation and the specific variant used in our algorithm. We will start by looking at the steps of the algorithm and later specify the conditional independency test employed.

The steps of the PC algorithm are described in Figure 3 where we can see that some steps offer a high degree of flexibility allowing different approaches. For example, in step 2) any conditional independency test would do, but also different orders of variable selection can be used. In our work we used the Fisher’s Z test and the simplest ordering, checking sequentially pairs of variables in the order variables appear in the dataset.

The Fisher's Z test was explained in detail in section 2.1.4.2. We used it with the parameter α[14] having value 0.05, meaning that the probability of incorrectly rejecting the null hypothesis is 5%. This is the most commonly used value and it will serve our purposes.

Steps 1) and 2) produce an undirected graph while steps 3) and 4) try to orient as many edges as possible. The inference of edge orientation through the knowledge present in the ontology could be done before step 1), after step 2), or as it will be in our case after the algorithm finishes.

Step 4) is also given in a descriptive way which allows us to take different approaches. It has been shown the four rules listed in Figure 4 are required for obtaining a maximally oriented PDAG. Moreover, they are sufficient, meaning that repeated application will eventually orient all edges which are common to the graph's equivalence class [39].

This algorithm works under the assumption of absence of *latent structures*[15]. They require a special treatment, because the constraints a latent structure imposes upon the distribution cannot be completely characterized by any set of conditional independence statements.

4.1.3 Node annotation

In order to use the PDAG produced from the previous step together with the ontology we need to make a connection between ontology concepts and the BN variables. As we have discussed earlier, this is done by assigning a set of ontology terms to each variable. We assume that there exists a mapping created by experts which faithfully resembles the state of the world for the domain of interest.

[14] Usually refered to as significance level.

[15] A latent structure is one having only a subset of variables observed. By making the above assumption we assume that the variables from the dataset are indeed all the variables present in the system being modeled. This is a strong assumption which is rarely true.

```
1) Form the complete undirected graph $C$ on the vertex set $V$.

2) $i = 0$.
   Repeat
       Repeat
           Select an ordered pair of variables $X$ and $Y$ that are adjacent in $C$ such
           that $Adjecencies(C, X)\setminus\{Y\}$ has cardinality greater than or equal to $i$,
           and a subset $S$ of $Adjecencies(C, X)\setminus\{Y\}$ of cardinality $i$, and if $X$ and
           $Y$ are d-separated given $S$ delete edge $X - Y$ from $C$ and record $S$ in
           $Sepset(X, Y)$ and $Sepset(Y, X)$;
       Until all ordered pairs of adjacent variables $X$ and $Y$ such that
       $Adjecencies(C, X)\setminus\{Y\}$ has cardinality greater than or equal to $i$ and all subsets
       $S$ of $Adjecencies(C, X)\setminus\{Y\}$ of cardinality $i$ have been tested for d-separation;

       $i = i + 1$;
   Until for each ordered pair of adjacent vertices $X$, $Y$, $Adjecencies(C, X)\setminus\{Y\}$ is of
   cardinality less than $i$.

3) For each triple of vertices $X, Y, Z$ such that the pair $X, Y$ and the pair $Y, Z$ are each
   adjacent in $C$ but the pair $X, Z$ are not adjacent in $C$, orient $X - Y - Z$ as $X \rightarrow Y \leftarrow Z$
   if and only if $Y$ is not in $Sepset(X, Z)$.

4) In the partially directed graph that results, orient as many of the undirected edges as
   possible subject to two conditions: any alternative orientation would yield a new v-
   structure; or any alternative orientation would yield a direct cycle.


$Adjecencies(C, X)$ – set of nodes adjacent to $X$ in graph $C$
$Sepset(X, Y)$ – set of node d–separating nodes $X$ and $Y$
```

Figure 3 - PC algorithm

1. Orient $Y - Z$ into $Y \rightarrow Z$ whenever there is an arrow $X \rightarrow Y$ such that X and Z are nonadjecent.
2. Orient $X - Y$ into $X \rightarrow Y$ whenever there is a chain $X \rightarrow Y \rightarrow Z$.
3. Orient $X - Y$ into $X \rightarrow Y$ whenever there are two chains $X - Z \rightarrow Y$ and $X - W \rightarrow Y$ such that Z and W are nonadjecent.
4. Orient $X - Y$ into $X \rightarrow Y$ whenever there are two chains $X - Z \rightarrow Y$ and $Y \rightarrow W \rightarrow Z$ such that Z and Y are nonadjecent and X and W are adjecent.

Figure 4 – PC algorithm rules

4.1.4 Inferring undirected edge orientation from the ontology

We discussed the idea behind this step in the section where we dealt with the reasoning process. There we considered only how to infer if there exists a causal relationship between two terms. But in our approach each variable is annotated with a set of terms. Therefore, to infer a causal relationship between two variables we will have to look for a presence of a causal relationship between every pair of terms the two variables are annotated with.

For example, for two variables X and Y, such that X is annotated with the set of terms $\{T_1, T_2\}$ and Y with the set of terms $\{T_3, T_4, T_5\}$ we will need to check for a causal relation between terms $< T_1, T_3 >, < T_1, T_4 >, < T_1, T_5 >, < T_2, T_3 >, < T_2, T_4 >, < T_2, T_5 >$. By doing this we will check only if $X \rightarrow Y$. Therefore, we will also need to check the inverse relation.

For performing the reasoning process we used the HermiT reasoner. Two other reasoners were tried, Pellet and TrOWL, but they did not perform as well as HermiT [12]. There are also other reasoners available but they either did not provide an API for Java[16] or were not publicly available.

When considering the DAG property of BNs we could conclude that after finding a causal relation between two terms we do not have to check the existence in the other direction. However, in an ontology it is not mandatory for relationships to be acyclic. The simplest examples are relations such as “friend of” and “sister of” which will be present both ways and thus form a cycle. But this is also the case for causal relationships such as “regulates”, present in the GO. Some genes are parts of regulatory mechanisms which involve loops.

One such mechanism is one where we have a gene that starts getting expressed because of the presence of some chemical in the cell body. This gene gets translated into a protein which also has the ability to promote the expression of a second gene. Once the concentration of the protein reaches the threshold value the second gene starts getting expressed. The protein encoded by the second gene on the other hand acts as a repressor for the expression of the first gene and therefore we have a regulation loop.

[16] Which was used for implementing the algorithm.

There is the possibility even of self-regulating loops, when a gene is involved in regulating its own activity. Even though such loops could be found in an ontology, this case won't be considered in our approach.

This kind of cyclic relations cannot be encoded in BNs because it lacks the ability of representing temporal/dynamic aspects of the system. To do so an extension of the BN model should be introduced. Even if were to allow this violation it would not be too concerning since we are only interested in learning the structure and not using the BN for probabilistic inference.

There is another question that needs to be raised, the one asking which edges should the algorithm try to orient. The simplest approach would be to assume that the constraint-based structure learning algorithm has found all the independencies and we are left to try orienting only the undirected edges. On the other hand, from the previous discussion we see that some orientations might not have been considered because they violate the acyclicity property. Therefore, it would be worthwhile to consider all edges at the same time validating the results of the PC algorithm. The problem with this approach is the complexity of task that will be considered in the following section. This is also the reason for not using this step before the PC algorithm.

In order to deal with the mentioned complexity the implementation of this step was done by parallelizing the process such that each thread deals with one edge. The speedup of this step is therefore proportional to the number of threads/processing units. The implementation code for this step is given in the appendix section 7.2.

4.2 Complexity analysis

Now that we have seen the steps of the algorithm in detail we are going to consider their computational cost. The complexity, both space and time, proved to be quite a challenge when dealing with real-world data. For example the number of genes that get represented as nodes in the BN from a microarray experiment is in order of thousands. In that case just fully connecting a graph proves to be a challenge space-wise. In this section we will also show some optimization steps taken in order to deal with such challenges.

However, in this work we will be considering just the complexity of the steps in our algorithm and not the complexity of tools used, such as the reasoner. Specifically for reasoners, their performance is usually compared empirically. Tests show that different reasoners perform differently for different ontologies [12]. In our case we have chosen the reasoner that was the easiest to integrate and the one best performing on the example we used.

4.2.1 PC algorithm complexity

We will start by considering the complexity of the PC algorithm. More precisely we are going to put an upper bound on it. If we take that the graph has n nodes and let k be the maximal degree of any node. In the worst case, in each iteration, no edge will get removed. Therefore in the i-th iteration we will have to check separation sets of cardinality i and for each of the $n * (n-1)$ pairs of variables there are $\binom{n-2}{i}$ candidate separation sets, which gives us a total of

$$n * (n-1) * \sum_{i=0}^{k} \binom{n-2}{i} \leq n * (n-1)^{k+1} \tag{16}$$

independency tests. Such worst case examples are highly unlikely to be found in any dataset and the average expected number of independency tests is much lower. Still, the complexity is polynomial, namely $O(n^{k+2})$.

For each independency test we use the Fisher's Z test calculated by the recursive formula

$$\hat{\rho}_{XY\cdot\boldsymbol{Z}} = \frac{\hat{\rho}_{XY\cdot\boldsymbol{Z}\setminus\{Z_0\}} - \hat{\rho}_{XZ_0\cdot\boldsymbol{Z}\setminus\{Z_0\}}\hat{\rho}_{Z_0Y\cdot\boldsymbol{Z}\setminus\{Z_0\}}}{\sqrt{1-\hat{\rho}^2{}_{XZ_0\cdot\boldsymbol{Z}\setminus\{Z_0\}}}\sqrt{1-\hat{\rho}^2{}_{Z_0Y\cdot\boldsymbol{Z}\setminus\{Z_0\}}}}. \tag{17}$$

Where $\boldsymbol{Z}$ is the separation set being considered in the i-th step and therefore having cardinality $|\boldsymbol{Z}| = i$. To calculate this value we need to recursively call three calculations of the coefficient with separation set having cardinality $i-1$. Thus we have

$$T_i = 3 \cdot T_{i-1}, \tag{18}$$

$$T_0 = 8 \cdot d, \tag{19}$$

and therefore

$$T_i = 3^i \cdot T_0, \tag{20}$$

$$T_i = 8 \cdot 3^i \cdot d. \tag{21}$$

Here d stands for number of data values for each variable (number of experiments) and T_i denotes the number of arithmetic operations needed for each independency test between two variables with a separation set of cardinality i.

As we can see the complexity when considering the number of arithmetic operations turns out to be exponential. On the other hand by looking at the recursive formula we see that the complexity can be dealt with if we introduce caching of results since there will be lots of calls to previously calculated values. For caching results a tree-like structure was implemented where each path represents a string of node ids and the value at each tree node the value of the calculated coefficient. The first and second node in the path are the X and Y variables being tested for independence and the rest of the tree nodes in the path stand for the nodes in the separation set.

This approach considerably reduces time complexity but also takes into consideration the space complexity because it is not feasible to cache all the possible results in memory. The algorithm designed this way has been able to deal with datasets with as many as 6000 variables in a reasonable amount of time (under 2 min). For comparison most of the publicly available constraint-based structure learning algorithms struggle with the subset of the same dataset having around 100 variables.

4.2.2 Ontology inference complexity

The complexity of annotating nodes with ontology terms is linear, straightforward to deduce and it will not be considered. On the other hand the complexity for the inference by means of the ontology was already hinted. Here we will just formalize it. Let m be the maximum number of ontology terms mapped to any variable. Then for u undirected edges we have to make at most

$$2 * u * m^2 * 3 \tag{22}$$

calls to the reasoner. The first factor stands for checking both orientations, the third factor tells the number of pairs of terms to be sought for a causal relationship, and the last factor is just the number of calls to the reasoner for retrieving superclasses and related terms.

Even though the number of calls to the reasoner is quite low, the reasoning process itself is quite time consuming, especially if the ontology being employed is big. Even though the performance drastically increases when the inference process gets parallelized, such that each edge is given its own thread, it still takes a lot of time to perform this step (several hours).

5 Example

Now that we have discussed the algorithm we can look at how it behaves on a real-life example. We have chosen the field of molecular biology because of the amount of standardized data publicly available, the number of high quality ontologies devised, and of course the importance of the field. The data we are going to use was produced by a microarray experiment concerning the yeast cell cycle. The motivation for using this dataset was the fact it has been used in a number of papers that tried to learn the interaction network of its genes [7, 11, 16, 18, 37, 44]. There are various approaches varying in methods used, while only a small involved causal Bayesian networks, even though they gave promising results [16, 37].

We will see a brief overview of the data, the ontology employed, and in the end the results produced by the algorithm. All the resources used are publicly available [61, 62, 63].

5.1 Resources

5.1.1 Yeast cell cycle dataset

This dataset was created as a comprehensive catalog of yeast genes whose transcript levels vary periodically within the cell cycle. The experiments were done under different conditions and monitored during equally spaced intervals[17]. In our work the temporal aspect of the experiments was not considered, as it was done in other related works, instead it was assumed that the values are independently drawn from an unknown distribution [16, 37].

The dataset came in an already preprocessed form. It underwent through some standard transformation processes and it was normalized. To correct for the missing values the kNNimpute algorithm was used as explained in a previous section. It contains 76 gene expression measurements of the mRNA levels of 6177 S. cerevisiae open reading frames. Only small number of them have been proven to be cell cycle regulated (~800) [44].

Most related works use even smaller subsets of the original dataset to test their algorithms. The only one that considered at least the 800 genes found to be cell cycle regulated was proposed by Friedman, Linial, Nachman, Pe'er but we were unable to get the results in a

[17] Different for each experiment.

machine readable format, only as an on-line interactive graph which would require a great amount of time in order to compare with our results [16].

These smaller datasets are those for which it was found to regulate the production of a certain important gene, regulating the cell cycle or which are known to be highly over or under expressed during a specific phase of the cell cycle [44].

5.1.2 Gene Ontology

We decided to use the Gene Ontology since it is one of the most actively used and maintained ontologies and thus providing high quality knowledge. It is part of a major bioinformatics initiative with the aim of standardizing the representation of gene and gene product attributes across species and databases. The project provides a controlled vocabulary of terms for describing gene product characteristics and gene product annotation data. It has developed three ontologies that describe gene products in terms of their associated biological processes, cellular components and molecular functions in a species-independent manner [61]. They cover three different domains:

- **cellular component**, the parts of a cell or its extracellular environment,
- **molecular function**, the elemental activities of a gene product at the molecular level, such as binding or catalysis, and
- **biological process**, operations or sets of molecular events with a defined beginning and end, pertinent to the functioning of integrated living units: cells, tissues, organs, and organisms.

In our example we used the biological processes ontology, being the one containing the "regulates" relation which can be easily attributed a causal interpretation. A biological process is series of events accomplished by one or more ordered sets of molecular functions. Examples of broad biological process terms are cellular physiological process or signal transduction. It can be difficult to distinguish between a biological process and a molecular function, but the general rule is that a process must have more than one distinct steps [61].

Other than the “regulates” relationship the biological processes ontology also contains two sub-relationships, namely “positively regulates” and “negatively regulates”. For our purposes we do not need to distinguish them since we are not interested in the functional form of the causal relationship but only in the structure of the causal network. On the other hand some more advanced approaches in the future whose goal goes beyond structure learning could use this additional knowledge.

The upside of the Gene Ontology from an epistemic point of view, of being organism-independent is also a downside from a practical point. When dealing with a single organism (which is usually the case) we have a much bigger ontology of what is actually needed which considerably affects the performance. Some organism-specific ontologies have been created but are much too simple and stripped from most of the useful relations present in the complete one.

In any case we can be sure that the evolution of the Gene Ontology hasn’t stopped, which is currently being updated on a daily basis, and that it might provide a great deal more of useful knowledge in the future. Moreover, there are many more ontologies being created that could be used for supporting causal network structure learning in other domains.

5.1.3 Annotations

For standardization purposes the GO consortium devised also an annotation format, namely the GAF, currently version 2.0. The format specifies information that needs to be provided for each annotation of a gene, e.g. the GO id, *evidence code* and name [61].

A GO annotation consists of a GO term associated with a specific reference that describes the work or analysis upon which the association between a specific GO term and gene product is based. Each annotation must also include an evidence code to indicate how the annotation to a particular term is supported. Although evidence codes do reflect the type of work or analysis described in the cited reference which supports the GO term to gene product association, they are not necessarily a classification of types of experiments/analyses. Note that these evidence codes are intended for use in conjunction with GO terms, and should not be considered in isolation from the terms. If a reference describes multiple methods that each provides evidence to make a GO annotation to a particular term, then multiple annotations with identical GO identifiers and reference identifiers but different evidence codes may be made [61].

The evidence or quality code describes the work or analysis upon which the association between a specific GO term and gene product is based e.g. manual, automatic or computer analysis. It has a number of possible values depending on the analysis type. Not all the codes have the same strength and there exists a hierarchy between them[18]. They range from manually curated annotations inferred by direct assays to automatically assigned annotations based on similarity searches. The former being a highly trusted one, while the latter the least dependable [61].

The annotations process, in our case, was implemented quite straightforward since we used a publicly available web service which for a given gene id returns its GO terms. The web service we used is provided by YeastMine [63] which is specialized for the Yeast (Saccharomyces cerevisiae) genome. During the annotation process we haven't considered the evidence code information, for lack of expertise in the bioinformatics domain and again for testing our approach on as much data as possible. This may turn out to be a shortcoming and a potential cause for inferring non-causal relationships. Yet, a simple extension would allow an expert to use the algorithm only with the evidence codes she finds fit.

The mapping can be also loaded from and saved to a file. In our case it we use a standard format specified by the GO Consortium, the GAF 2.0 annotation file format.

5.2 Results

Here we will look at the resulting graphs produced by our algorithm. They have been produced on different subsets of the yeast cell cycle dataset and compared to other approaches. It wasn't possible to compare the graph resulting from the complete dataset since no other algorithm was able to deal with such an amount of data. Before we continue, we will pose some questions that will guide our review. The questions are the following:

[18] It can be seen in the appendix.

- Is it possible to find the orientation of undirected edges by reasoning over an ontology?
- Are the orientations sound?
- How do the results compare to other approaches?
- Is the process feasible on a larger scale?

5.2.1 Algorithm performance

In our first experiment we used a dataset made up from the 800 genes found to be cell cycle regulated. All the 76 data values for different experiments have been used and treated as independent observations. The PC algorithm ran for around 4 seconds and produced a graph with 132 undirected edges and 1251 directed ones. The annotation step assigned a total of 3072 terms to the 800 variables making an average of 3.84 terms per variable. The annotation was done by using a mapping file, after which the undirected edges were checked for causal relations between the incident variables. As a result 4 undirected edges have been oriented, one of which have been found to be bidirectional. Since we know the data to be temporal in its essence we cannot resolve these ambiguities. The step took around 2 hours and 27 minutes to complete while being executed in parallel on 3 threads.

From this information we can answer the first and last question. Yes, it is possible to infer the orientation of some undirected edges and in a similar manner it would be possible to validate the orientations found in the previous steps. But it is clear that the computational power needed for performing such an inference, which has resulted in the orientation of only a small fraction of undirected edges, is more than we would expect to spend for such a procedure. Especially when knowing that much quicker results could be produced by some other methods even when sacrificing correctness. As always it is a matter of our needs and the trade-off we are willing to make.

5.2.1.1 Soundness

To see whether the orientations inferred using the ontology are sound we will inspect the ontology to see if the semantics of the gene annotations match causal relations. We will look at two cases:

- when an undirected edge between A and B gets directed into $A \rightarrow B$;
- when an undirected edge between A and B gets directed into $A \leftrightarrow B$.

For the first case genes $YGR108W$ and $YGL021W$ will be considered whose annotation can be seen in Table 1, while part of the ontology is shown in Figure 5. In the red area we can see some of the $YGR108W$ gene terms and in the green one some terms related to the $YGL021W$ gene.

Table 1 – YGR108W and YGL021W annotations

Gene id	GO term id	GO term name	Evidence code
$YGR108W$	GO_0000079	regulation of cyclin-dependent protein kinase activity	IMP
	GO_0000086	G2/M transition of mitotic cell cycle	IMP
	GO_0007049	cell cycle	IEA
	GO_0007067	mitosis	IEA
	GO_0008315	meiotic G2/MI transition	IMP
	GO_0010696	positive regulation of spindle pole body separation	IGI
	GO_0030472	mitotic spindle organization in nucleus	IMP
	GO_0051301	cell division	IEA
	GO_0051726	regulation of cell cycle	IEA
$YGL021W$	GO_0006468	protein phosphorylation	IDA
	GO_0006974	response to DNA damage stimulus	IEA
	GO_0007049	cell cycle	IEA
	GO_0007067	mitosis	IEP
	GO_0016310	phosphorylation	IEA

As we can see the terms overlap and we could expect to find a self-regulatory loop if we were to consider it. The nodes acting as end points of "regulates" relations have a straightforward semantic relation to the starting nodes ("cellular process", "regulation of cellular process”). The rightmost regulatory relation is the one upon which the causal relation between the two genes would be inferred. Other regulatory relations would not be considered since starting from superclasses of their terms.

If we were to consider the relations between the other terms no new regulatory relations would be found and therefore no other orientation, other than the so far discussed, would be found. Therefore the edge was oriented as $YGR108W \rightarrow YGL021W$ and based on the semantics of the term names we can conclude that such an orientation is sound under the assumption that the ontology and the annotations reflect the real sate of the world.

Unfortunately if we were to consider the interaction networks of the two genes we would find no interactions between them as shown in Figure 6 [63]. Therefore, either the algorithm has found a new interaction or the structure found is wrong. For the latter case, the reason for the error is twofold. Firstly, the PC algorithm found the genes to be dependent which is not the case. Secondly, the evidence codes, which can be seen in Table 1, are of the lowest confidence level and being automatically assigned it is possible that in the future they will be proved to be incorrect. On the other hand in case of finding strong evidence for the given annotation it would imply the need for updating the interaction network.

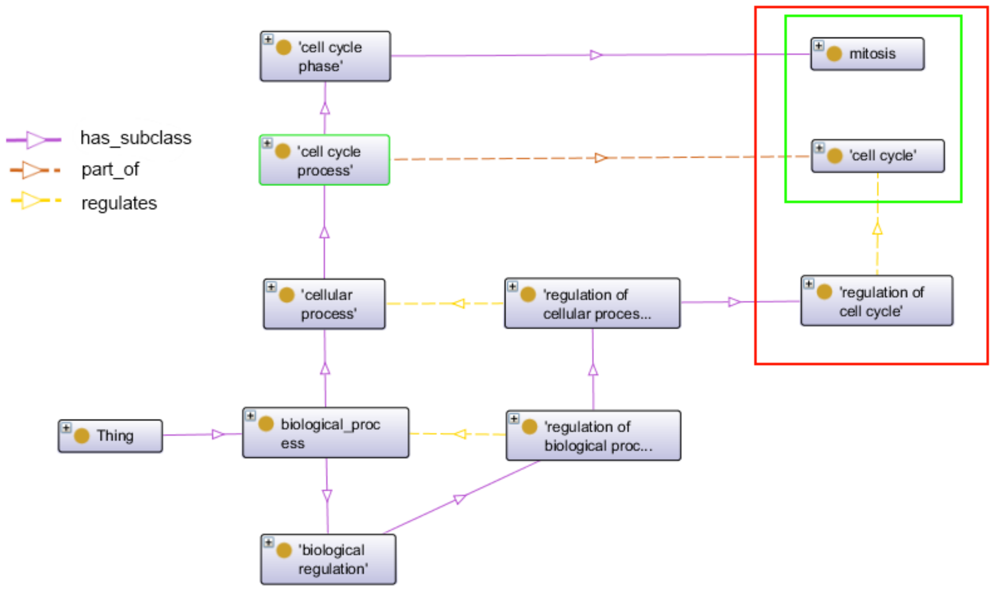


Figure 5 - Ontology fragment

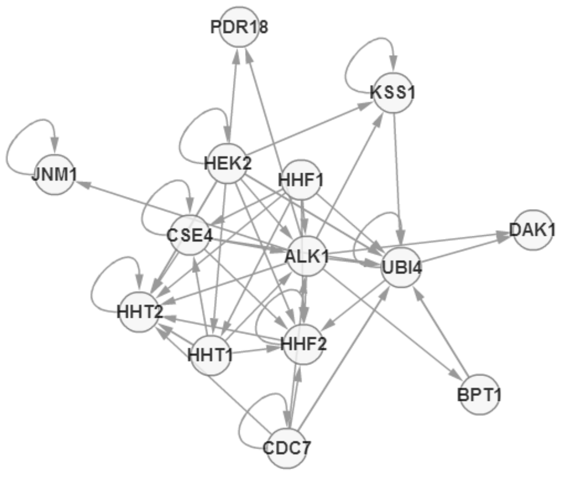


Figure 6 - YGL021W (ALK1) interaction network

The other case we are about to explore deals with edges found to be bidirectional for which we will try to give biological interpretation/justification. In the current example the genes found to be involved in such way are $YCR040W$ and $YCL066W$. The first thing to notice for these two genes is that they are annotated by the same terms which incited us to look deeper in their biological role. As it turns out the latter is just a silenced copy[19] of the former one, and therefore these genes are not part of a regulatory cycle which can be also seen by looking at their interaction networks, shown in Figure 7 [63].

Again if we were to look at the evidence codes for the annotation terms, the ones implying a causal relationship have poor evidence codes and therefore the same discussion presented above would apply. However, the PC algorithm in this case has correctly inferred the correlation between the two genes since they are equal sequences encoding the same gene, where one is just a silenced copy of the other. Such genes, having the same amino-acid sequence, would have the same expression levels in a microarray experiment and therefore their correlation is inevitable. The best way to treat such variables would be to eliminate one, since in this experiment they cannot be told apart.

[19] The exact copy of the gene's amino-acid sequence which is present in the genetic code for the purpose of preserving genetic material. Usually present in cases where there exists an alternative silenced gene that gets, given the right setting, expressed instead.

If we were to look at the two genes as being the same node it would turn out to be a self-regulatory node which would not be considered by our algorithm.

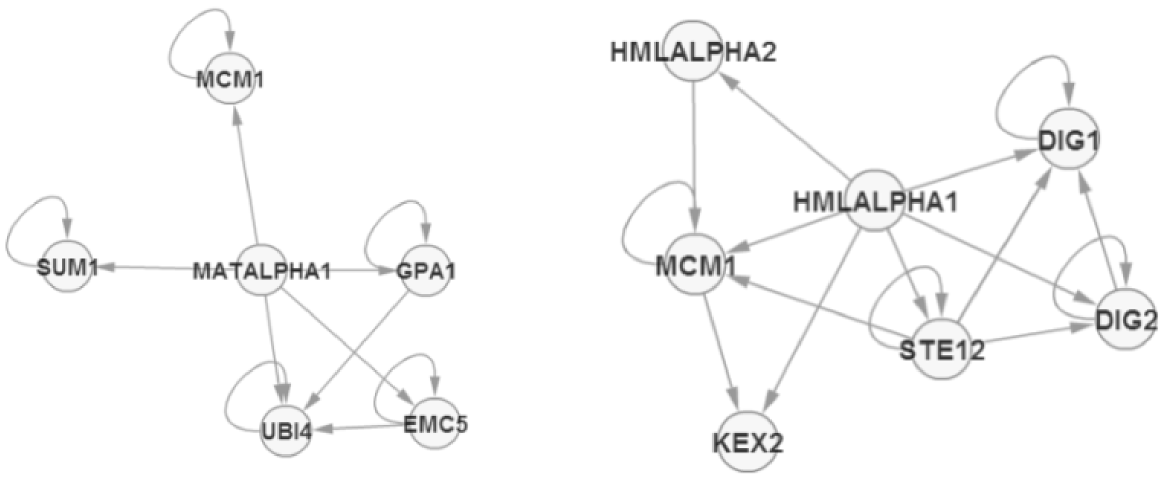


Figure 7 - YCR040W (MATALPHA1) and YCL066W (HMLAPHA1) interaction networks

The considerations made so far show the importance of the knowledge used for inferring the network structure. Since we rely on assumption that it reflects the true state of the world, the produced network is sound under the given assumption. This we saw to be reflected in the semantics of the ontology terms. The difference between this and other manual approaches is that our algorithm relies on publicly available and constantly changing data used also for other purposes. This does not require a domain expert being present every time a network needs to be constructed but only experts curating publicly available knowledge, which in this case comes in the form of an ontology and the annotation mappings.

5.2.2 Comparison to other approaches

Now we are left with answering the last question left unanswered which requires comparing our algorithm to other approaches. Even though the motivation for using the proposed dataset was because it was referenced by a number of papers dealing with Bayesian network structure learning, none provide a machine readable BN with all the 800 cell cycle regulated genes. Most of them deal with only small subset of nodes. For the comparison we decided to use some of the algorithms made publicly available and compare their resulting graphs with ours on a randomly chosen subset of the Spellman dataset containing 50 genes.

Some of the algorithms might perform poorly because needing data discretization and we cannot guarantee that the discretization parameters used are the optimal for the given dataset and algorithm. Another factor that should be taken into account is that some algorithms, especially the score-based ones, are nondeterministic in nature and might not give the same answer each time. In our case, the relatively small number of variables taken into account has proven to produce the same structure on different runs which made it easier to analyze the results.

Two main characteristics of the resulting graphs will be in our focus: the degree of similarity of the resulting graphs' skeletons and the degree of similarity of edge orientations. This will be done by counting the number of edges the graphs agree and disagree upon, for both characteristics.

The comparison will be performed with both score-based and constraint-based approaches which are listed below. A difference between these algorithms is one that we have already seen earlier but it is worth repeating, namely that constraint-based algorithms in general produce partially oriented graphs, while score-based always produce totally oriented graphs.

- Constraint-based: *Grow-Shrink*, *Incremental Association (IA), PC with discrete data*
- Score-based: *Hill-Climbing (HC) with continuous data, Hill-Climbing with discrete data, Tabu search*

All of the above algorithms were run on the same computer and took a couple of seconds to finish, except for our approach which took under a second for the step involving the PC algorithm and a couple of minutes for the ontology inference step.

The results are shown in tables 2, 3 and 4. Table 2 shows number of edges found by the algorithms, from which we can read out that score-based algorithms prefer highly connected structures. Such structures are not expected when considering causal networks, for which we expect that each effect has only a small number of direct causes. On the other hand, constraint-based algorithms seem to form reasonable structures except maybe for the PC algorithm with discrete variables, probably affected by the discretization step. Moreover, the IA algorithm proved to perform quite poorly in the edge-orienting phase.

Table 2 - Number of edges found

Algorithm	Directed edges found	Undirected edges found	Total
Our approach	67	5	72
Grow-Shrink	40	2	42
IA	4	55	59
PC (discrete)	21	0	21
HC (discrete)	86	0	86
HC (continuous)	220	0	220
Tabu	220	0	220

Tables 3 and 4 show the similarity measures between the resulting graph of the respective algorithm and the one produced by our approach. The ratio indicates the number of edges the graphs have in common with respect to the total number of edges. Each of the two characteristics of interest takes into consideration different sets of edges. When considering the skeleton similarity we disregard the edge orientation and just look for the number of edges present in the intersection of the sets of edges with respect to the number of edges present in their union. Orientation similarity on the other hand takes into consideration only directed edges and counts the edges present in both skeletons and having the same orientation.

Table 3 - Constraint-based algorithms

	Grow-Shrink	IA	PC (discrete)
Skeleton	28/87 (31.0%)	41/90 (45.6%)	14/79 (17.7%)
Orientation	10/80 (12.5%)	1/70 (1.4%)	4/74 (5.4%)

Table 4 - Score-based algorithms

	HC (discrete)	HC (continuous)	Tabu
Skeleton	29/129 (22.5%)	62/230 (27.0%)	62/230 (27.0%)
Orientation	15/124 (12.1%)	22/225 (9.8%)	22/225 (9.8%)

As expected the similarities are higher for the skeletons than for the orientations. This is because orientation similarity along with the skeleton similarity also requires the orientations to agree. The similarity in the number of edges makes the constraint-based approaches' graphs have a greater structural similarity with the ones produced by our approach. On the other hand the high number of oriented edges present in the graphs of score-based approaches has the consequence that the two compared graphs share a higher number of edges and are more likely to agree on their orientation. This comes with the cost of a less similar structure.

A closer look to the edges between specific nodes reveals that the edge orientations inferred by the ontology are usually in accordance with the ones found by other algorithms. In one case, three algorithms are in accordance with the findings, two disagree on the orientation, one did not orient the edge, and one did not have the edge in its structure. In the other case four agree on the orientation, and two do not contain the edge in question.

Unfortunately in this work we will not compare the results to some known causal structure for the given genes. Such a comparison would require a deeper knowledge of the domain since there exist some graphs representing the relations between the genes but their semantics was not understood properly enough in order to draw conclusions.

5.3 Discussion

Now that we have seen the answers to all the posed questions we are ready to put things in perspective. We can see that our approach is a valid one with sound results in the chosen domain, but at the same time it is easy to see that the approach is domain independent.

Comparison to other approaches has proven to be hard because of two reasons. The first one being that other approaches were able to handle only small fragments of the entire dataset and thus not allowing a full scale comparison. Either the space requirements at some point of the execution of the algorithm would exceed the available amount of memory, or when the data was scaled to overcome the memory problem the execution had to be interrupted because exceeding the amount of time set as the threshold (several hours, whereas our approach would end in matter of seconds).

The second reason has to do with the degree of similarity of the resulting graphs, which has proven to be quite low. Each algorithm resulted in completely different network structure, i.e. different set of independence statements. With such a difference in the results it is hard to justify any of them. It is reasonable to ask, why do we get such different results? Especially when trying to infer causal relations which are of particular interest exactly because of their stability. The best answer we can give as of now is that we lack data, and that the 76 data points at our disposal are not enough for inferring stable causal relations. On the other hand the lack of data, which is usually expensive to gather, is the trademark of real world settings and our main goal is trying to devise an approach that could exploit the small amount of data at our disposal to infer the underlying causal relations.

This is where our approach differs from others, it exploits publicly available knowledge of the domain, which is also known to incorporate causal knowledge about its terms. The downside is that inferring the needed relations from such knowledge is not easy and for now it is a quite slow process. On the other hand the main advantage is that if the knowledge source, in our case an ontology, is assumed to reflect the true state the real world, we can regard the knowledge transferred to our network as stable, which gives us the needed property for giving the resulting network a causal interpretation.

Another consideration which was mentioned earlier but that maybe has not been stressed enough is the fact that even though we used a specific constraint-based algorithm, namely the PC algorithm, as a base for our approach it could be replaced by any other algorithm. The PC algorithm is in itself quite a simple approach and in the meanwhile more advanced algorithms have been devised which could, coupled with the ontology-driven phase, give better results.

The possible extensions of our approach and other considerations will be left for the next section.

6 Conclusion

We have showed in detail the idea behind our approach, how it performs on a real-world dataset and how it compares to other approaches. Throughout this work we stated the assumptions needed for the approach to work and in the discussion given in the previous chapter we covered the pros and cons inherent in our approach.

To conclude, we can state that our idea does provide a valid approach for the problem of causal Bayesian network structure learning. Even though it did not excel on the example considered in this work it is likely that it would perform better on some other dataset or given a better mapping between the ontology terms and the variables. Besides that, the knowledge transferred from the ontology can be regarded as reflecting the true state of the world, which provides the needed guarantee for interpreting the resulting Bayesian network as causal one.

On the other hand, some open issues remain. The time required for inferring relations in the ontology is too high compared to what we would like to see when considering practical applications. Also, the mapping of the ontology terms to variables might have to be performed manually for most of the domains which would make the algorithm outside of the molecular biology domain semi-automatic. Another issue worth considering is whether it is possible to decide which relations defined in the ontology have causal semantics and in which way do they relate to other relations, e.g. do they form property chains.

Future works based on this approach can go different ways. One direction is the optimization of the step for inferring the edge orientation. Other approaches could consider placing the mentioned step at some other point of the structure learning process or using it for checking and updating the structure found by the base algorithm. Yet another direction could consider an in-depth analysis of the base structure learning algorithm focused on finding one that either gives an overall better performance than the PC algorithm used or one which integrates better with the step involving ontology inferrence. As last we will also mention the possibility of considering different types of Bayesian networks, such as object-oriented and hierarchical Bayesian networks.

7 Appendix

7.1 Relation properties

Some important properties of binary relations:

Reflexivity: $\forall a : aRa$

Irreflexivity: $\forall a : \neg(aRa)$

Symmetry: $\forall a, b : aRb \rightarrow bRa$

Asymmetry: $\forall a, b : aRb \rightarrow \neg(bRa)$

Antisymmetry: $\forall a, b : aRb \wedge bRa \rightarrow a = b$

Transitivity: $\forall a, b, c : aRb \wedge bRc \rightarrow aRc$

Intransitivity: $\neg\forall a, b, c : aRb \wedge bRc \rightarrow aRc$

7.2 Ontology inference step code

In this section of the appendix we can see the Java code implementation of the ontology inference step used for inferring a causal relation between two graph nodes (variables). The full code will be made available upon request.

```
public class CausalInference extends Thread
{
	// List of newly oriented edges.
	private List<Touple<Integer, Integer>> inferedDirections;
	// The reasoner used for the inference process.
	private Reasoner reasoner;
	// Variable being considered to be the potential cause.
	private NodeItem cause;
	// Variable being considered to be the potential effect.
	private NodeItem effect;

	/**
	 *  Constructor
	 * @param reasoner    The reasoner to be used for the inference
	 * @param ontology    The ontology name to be used
	 * @param cause       Potential cause
	 * @param effect      Potential effect
	 */
	public CausalInference(Reasoner reasoner, NodeItem cause, NodeItem effect)
	{
		super("Causal inference");
		this.reasoner = reasoner;
		this.cause = cause;
		this.effect = effect;
```

```java
}

/**
 * Starts the thread and passes the current list of newly
 * directed edges.
 * @param inferedDirections  List of newly directed edges
 */
public void run(List<Touple<Integer, Integer>> inferedDirections)
{
       this.inferedDirections = inferedDirections;
       start();
}

/**
 * The main method of the causal inference process. It
 * performs the steps described in the work to find out
 * if there exists a causal relation from the "cause"
 * and "effect" variable.
 */
@Override
public void run()
{
       // The lists of annotations for the respective variables.
       List<String> causeAnnotations = cause.getAnnotations(ontologyName);
       List<String> effectAnnotations = effect.getAnnotations(ontologyName);
       // In case that either list of annotations is empty there is no
       // reasoning to be done and the method exits.
       if(causeAnnotations.isEmpty() || effectAnnotations.isEmpty())
       {
              returnReasoner();
              return;
       }

       // Set of the OWL terms of the cause variable.
       Set<OWLClassExpression> causeTerms = new HashSet<OWLClassExpression>();
       for(String causeTermId : causeAnnotations)
       {
              causeTerms.add(dataFactory.getOWLClass(IRI.create(GeneOntology.prefix
                                                                  + causeTermId)));
       }

       // The OWL property expression for the causal relation
       OWLObjectPropertyExpression causallyRelates = dataFactory.getOWLObjectProperty(
                                                    IRI.create(Ontology.this.causalRelation));

       // OWL expression of terms causally influencing terms of the effect
       variable.
       OWLClassExpression causallyInfluencingTerms;
       // Term of the effect variable considered.
       OWLClass causallyInfluencedTerm;
       // Set of all the terms causally influencing the effect variable's term.
       Set<OWLClassExpression> termSetCausallyInfluencingEffect = new
                                                           HashSet<OWLClassExpression>();

       // Loops through all the terms in the effect variable's annotations,
       // infers all the terms causally influencing each of them, and adds
       // them to the specified set.
       for(String annotation : effectAnnotations)
       {
              causallyInfluencedTerm = dataFactory.getOWLClass(IRI.create(
                                                           ontologyPrefix + annotation));
```

```
                causallyInfluencingTerms = dataFactory.getOWLObjectSomeValuesFrom(
                                    causallyRelates, causallyInfluencedTerm);

                // Loops through all the terms causally influencing the current
                // term (from the effect variable's annotations).
                for(Node<OWLClass> regulatingGene :
                        reasoner.getSubClasses(causallyInfluencingTerms, true))
                {
                        termSetCausallyInfluencingEffect.add(
                                        regulatingGene.getRepresentativeElement());
                }
        }

        // Looks for the intersection between the terms causally influencing
        // the effect variable's terms and cause's terms.
        List<OWLClassExpression> intersection = intersectionOf(causeTerms,
                                    termSetCausallyInfluencingEffect);

        // In case the intersection is not empty there exists a causal
        // relation from the cause to the effect variable.
        if(!intersection.isEmpty())
        {
                synchronized (inferedDirections)
                {
                        inferedDirections.add(new Touple<Integer, Integer>(cause.getId(),
                                                                effect.getId()));
                }
        }

        // Returns the reasoner to the reasoner pool.
        returnReasoner();
    }

    /**
     * Returns the reasoner to the reasoner pool.
     */
    private void returnReasoner()
    {
        synchronized (reasoners)
        {
                reasoners.add(this.reasoner);
                reasoners.notify();
        }

    }
}
```

7.3 Evidence codes

The **experimental** evidence codes are:
Inferred from Experiment (EXP)
Inferred from Direct Assay (IDA)
Inferred from Physical Interaction (IPI)
Inferred from Mutant Phenotype (IMP)
Inferred from Genetic Interaction (IGI)
Inferred from Expression Pattern (IEP)

The **computational analysis** evidence codes are:
Inferred from Sequence or structural Similarity (ISS)
Inferred from Sequence Orthology (ISO)
Inferred from Sequence (ISA)
Inferred from Sequence Model (ISM)
Inferred from Genomic Context (IGC)
Inferred from Biological aspect of Ancestor (IBA)
Inferred from Biological aspect of Descendant (IBD)
Inferred from Key Residues (IKR)

The **author statement** evidence codes used by GO are:
Traceable Author Statement (TAS)
Non-traceable Author Statement (NAS)

The **curatorial statement** codes are:
Inferred by Curator (IC)
No biological Data available (ND)

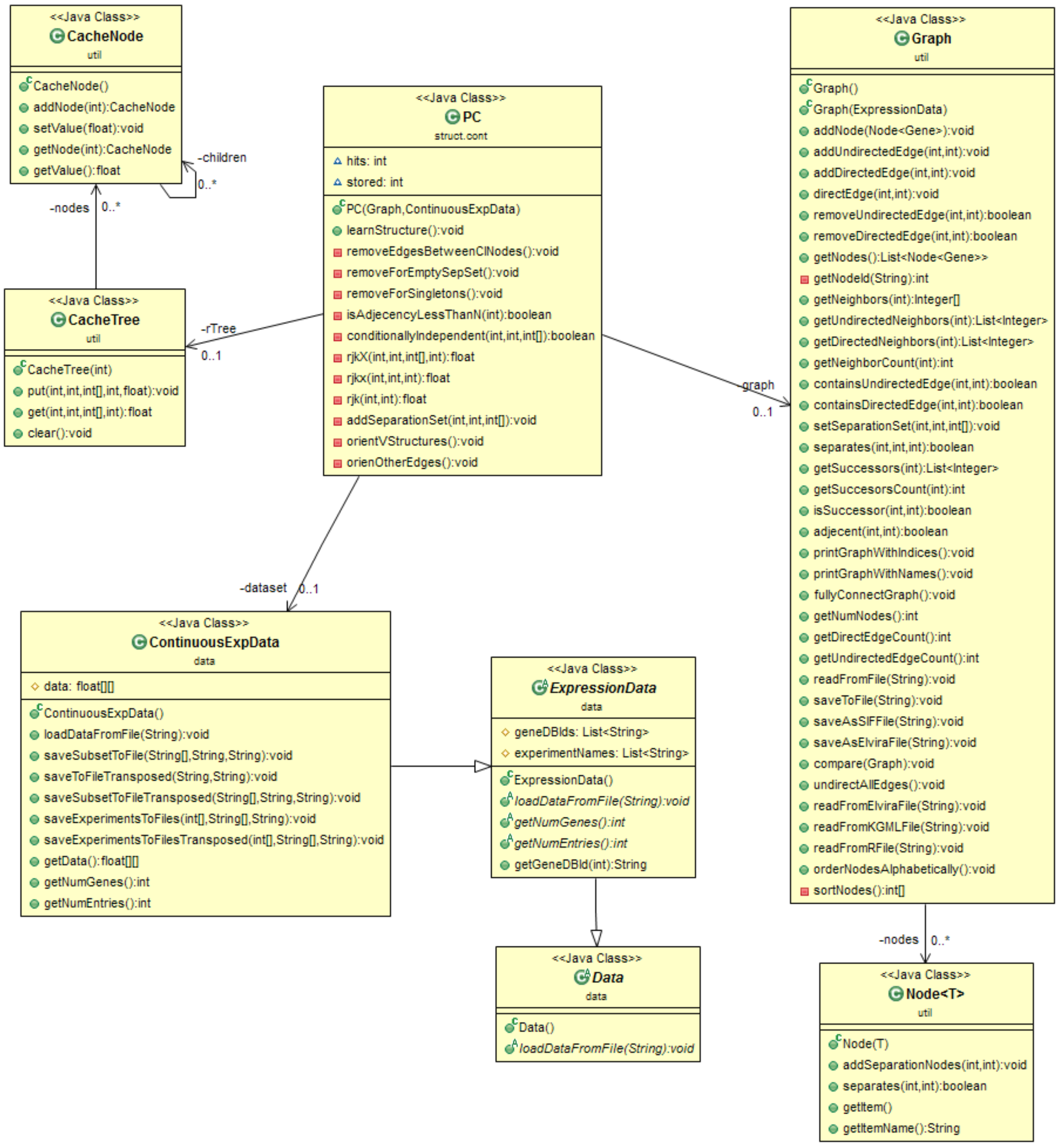
The **automatically-assigned** evidence code is:
Inferred from Electronic Annotation (IEA)

The evidence codes can be thought of in a loose hierarchy of reliability, part of it would be the following:

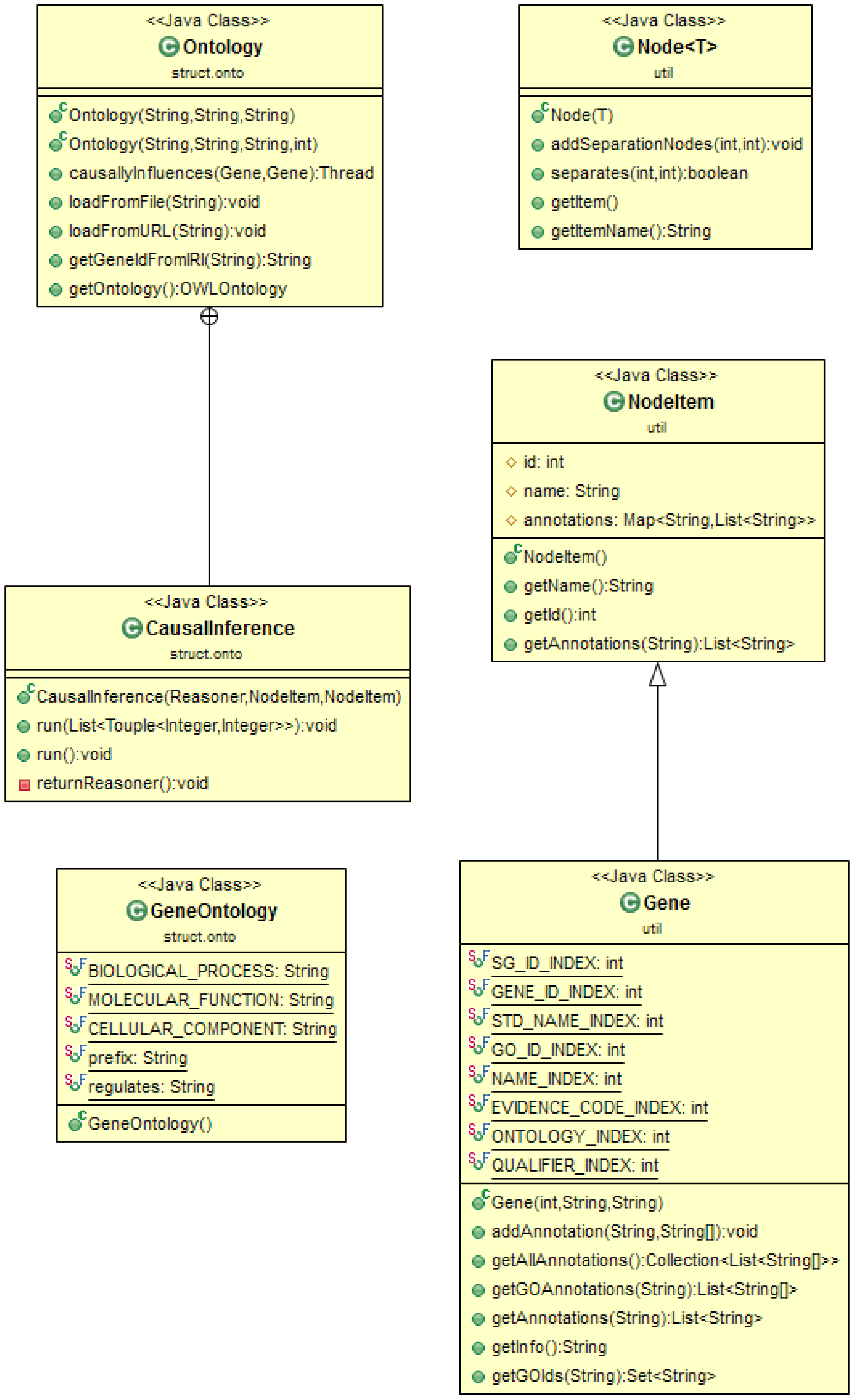
1. TAS/IDA
2. IMP/IGI/IPI
3. ISS/IEP
4. NAS
5. IEA

This hierarchy should not be interpreted as a rigid ranking of evidence types. The users can and should form their own conclusions as to the reliability of each type of evidence and each individual annotation. It is a loose hierarchy also partly because the strength of the evidence will also depend on to what resolution is being annotated, and because there is a range of reliability within each evidence category.

7.4 Class diagrams



<<Java Class>>
CacheNode
util
CacheNode()
addNode(int):CacheNode
setValue(float):void
getNode(int):CacheNode
getValue():float
-children
0..*
-nodes
0..*
<<Java Class>>
CacheTree
util
CacheTree(int)
put(int,int,int[],int,float):void
get(int,int,int[],int):float
clear():void
-rTree
0..1
<<Java Class>>
PC
struct.cont
hits: int
stored: int
PC(Graph,ContinuousExpData)
learnStructure():void
removeEdgesBetweenCINodes():void
removeForEmptySepSet():void
removeForSingletons():void
isAdjecencyLessThanN(int):boolean
conditionallyIndependent(int,int,int[]):boolean
rjkX(int,int,int[],int):float
rjkx(int,int,int):float
rjk(int,int):float
addSeparationSet(int,int,int[]):void
orientVStructures():void
orienOtherEdges():void
graph
0..1
<<Java Class>>
Graph
util
Graph()
Graph(ExpressionData)
addNode(Node<Gene>):void
addUndirectedEdge(int,int):void
addDirectedEdge(int,int):void
directEdge(int,int):void
removeUndirectedEdge(int,int):boolean
removeDirectedEdge(int,int):boolean
getNodes():List<Node<Gene>>
getNodeId(String):int
getNeighbors(int):Integer[]
getUndirectedNeighbors(int):List<Integer>
getDirectedNeighbors(int):List<Integer>
getNeighborCount(int):int
containsUndirectedEdge(int,int):boolean
containsDirectedEdge(int,int):boolean
setSeparationSet(int,int,int[]):void
separates(int,int,int):boolean
getSuccessors(int):List<Integer>
getSuccesorsCount(int):int
isSuccessor(int,int):boolean
adjecent(int,int):boolean
printGraphWithIndices():void
printGraphWithNames():void
fullyConnectGraph():void
getNumNodes():int
getDirectEdgeCount():int
getUndirectedEdgeCount():int
readFromFile(String):void
saveToFile(String):void
saveAsSIFFile(String):void
saveAsElviraFile(String):void
compare(Graph):void
undirectAllEdges():void
readFromElviraFile(String):void
readFromKGMLFile(String):void
readFromRFile(String):void
orderNodesAlphabetically():void
sortNodes():int[]
-dataset
0..1
<<Java Class>>
ContinuousExpData
data
data: float[][]
ContinuousExpData()
loadDataFromFile(String):void
saveSubsetToFile(String[],String,String):void
saveToFileTransposed(String,String):void
saveSubsetToFileTransposed(String[],String,String):void
saveExperimentsToFiles(int[],String[],String):void
saveExperimentsToFilesTransposed(int[],String[],String):void
getData():float[][]
getNumGenes():int
getNumEntries():int
<<Java Class>>
ExpressionData
data
geneDBIds: List<String>
experimentNames: List<String>
ExpressionData()
loadDataFromFile(String):void
getNumGenes():int
getNumEntries():int
getGeneDBId(int):String
<<Java Class>>
Data
data
Data()
loadDataFromFile(String):void
-nodes
0..*
<<Java Class>>
Node<T>
util
Node(T)
addSeparationNodes(int,int):void
separates(int,int):boolean
getItem()
getItemName():String



<<Java Class>>
Ontology
struct.onto
Ontology(String,String,String)
Ontology(String,String,String,int)
causallyInfluences(Gene,Gene):Thread
loadFromFile(String):void
loadFromURL(String):void
getGeneIdFromIRI(String):String
getOntology():OWLOntology
<<Java Class>>
Node<T>
util
Node(T)
addSeparationNodes(int,int):void
separates(int,int):boolean
getItem()
getItemName():String
<<Java Class>>
NodeItem
util
id: int
name: String
annotations: Map<String,List<String>>
NodeItem()
getName():String
getId():int
getAnnotations(String):List<String>
<<Java Class>>
CausalInference
struct.onto
CausalInference(Reasoner,NodeItem,NodeItem)
run(List<Touple<Integer,Integer>>):void
run():void
returnReasoner():void
<<Java Class>>
GeneOntology
struct.onto
BIOLOGICAL_PROCESS: String
MOLECULAR_FUNCTION: String
CELLULAR_COMPONENT: String
prefix: String
regulates: String
GeneOntology()
<<Java Class>>
Gene
util
SG_ID_INDEX: int
GENE_ID_INDEX: int
STD_NAME_INDEX: int
GO_ID_INDEX: int
NAME_INDEX: int
EVIDENCE_CODE_INDEX: int
ONTOLOGY_INDEX: int
QUALIFIER_INDEX: int
Gene(int,String,String)
addAnnotation(String,String[]):void
getAllAnnotations():Collection<List<String[]>>
getGOAnnotations(String):List<String[]>
getAnnotations(String):List<String>
getInfo():String
getGOIds(String):Set<String>

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