Scalable Causal Structure Learning: New Opportunities in Biomedicine

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Abstract
This paper gives a practical tutorial on popular causal structure learning models with examples of real-world data to help healthcare audiences understand and apply them. We review prominent traditional, score-based and machine-learning based schemes for causal structure discovery, study some of their performance over some benchmark datasets, and discuss some of the applications to biomedicine. In the case of sufficient data, machine learning-based approaches can be scalable, can include a greater number of variables than traditional approaches, and can potentially be applied in many biomedical applications.

Keywords: causal inference, causal structure discovery;

1 Introduction

Causal structure learning refers to the problem of identifying the causal structure from observed data. The causal structure is represented by a causal graph (also called a causal Bayesian network), which is a directed acyclic graph (DAG), in which the nodes represent variables and edges represent causation (Fig. 1). An edge is drawn from a variable that represents the cause to a variable that represents the effect of that cause. For example, consider the example of a gene regulatory network[1–4], which is an abstract representation of the complex biophysical processes as shown in Figure 1.

The problem of learning an acyclic causal structure from data, which is in general NP-complete [5], has been studied for a long time [6]. Traditionally, constraint-based and score-based methods which usually search for the optimal graph from a discrete space of candidate graphs, have been used to learn the DAG from data. Constraint-based methods such as the PC and fast causal inference (FCI) algorithm rely on statistical tests to estimate the correct causal structure. This was followed by research on score-based methods, which assign scores based on the data to each DAG and select the one with the best score. With the advent of big data, recent research has also focused on finding an optimal graph from the continuous space of weighted
DAGs, by converting the combinatorial acyclicity constraint into an equality constraint involving a smooth nonlinear acyclicity function. This enables the use of machine learning and deep learning algorithms in finding the optimal causal structure. Table 1 summarizes the algorithms that we will discuss.

**Figure 1.** (a) A gene regulatory network is an abstracted structure (given by the directed graph on the right) of the complex biophysical process shown on the left. (b) A gene regulatory structure from the *transmir* database for mice.
**Contributions.** This paper attempts to provide a comparative study of various algorithms that are used to discover causal structure from observational data to the biomedicine community. These algorithms could offer biomedicine communities viable research ideas in causal structure learning, in addition to popular association-based methods. Some of these traditional and score-based methods have been studied extensively[7], but many of the algorithms discussed here employ machine learning techniques, which makes them scalable in the age of big and higher-dimensional data. Although we do not list all possible approaches like Vowels et al.[8], we sample a few important algorithms and evaluate their performance on synthetic datasets and the Sachs dataset[9].

**Paper organization.** This tutorial paper will present algorithms for causal structure identification and example applications within the field of medical informatics. In Section 2, we examine algorithms that determine the optimal causal graph in discrete space. In Section 3, we discuss computational algorithms that use continuous space optimization to discover causal relationships. We compare the performances of these algorithms in Section 4. Lastly, we present the discussion in section 5.

## 2 Causal Structure Discovery: Discrete Space Algorithms

This section discusses discrete space algorithms for causal discovery, i.e., algorithms that search for the optimal DAG in the discrete space of candidate causal graphs.

| Algorithm | Summary |
|-----------|---------|
| PC (named after Peter Spirtes and Clark Glymour) | A partially directed acyclic graph (CPDAG) is produced by iteratively checking the conditional independence conditions of adjacent nodes, conditioned on an all-size subset of neighbors |
| IC (Inductive Causation) | Returns the equivalent class of the DAG, based on the estimated probability distribution of random variables and an underlying DAG structure |
| FCI (Fast Causal Inference) | Modified PC algorithm to detect unknown confounding variables and produces asymptotically correct results. |
| Method                                      | Description                                                                                                                                                                                                 |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| GES (Greedy Equivalence Search)             | Starts with an empty graph and iteratively adds and deletes edges in the graph by optimizing a score function.                                                                                               |
| Fast GES                                    | Improved and parallelized version of GES                                                                                                                                                                    |
| K2                                          | Perform a greedy heuristic search for the parents of each node.                                                                                                                                              |
| Max-Min Hill Climbing (MMHC)                | Max-Min Hill Climbing (MMHC) to find the skeleton of the Bayesian network followed by constrained greedy search to orient the edges.                                                                        |
| LiNGAM (Linear Non-Gaussian Acyclic Model)  | Transfer the linear structure model $x_i = \sum_{j<i} b_{ij} x_j + e_j$ to the form of $x = Bx + e$, and optimize for matrix $B$.                                                                           |
| NOTEARS                                     | Uses smooth function $h(A)$, whose value characterizes the “DAG-ness” of the graph with adjacency matrix $A$ ($h(A)=0$ for DAG), and optimizes using continuous optimization.                                             |
| NOBEARS                                     | Proposed a new constraint as compared to NOTEARS, which allows for faster optimization and scalability, and a polynomial regression loss infer gene regulatory networks from nonlinear gene expressions. |
| DAG-GNN                                     | Uses an autoencoder framework, and uses deep learning to train it and infer the causal structure from the weights of the trained network, and is more scalable than NOTEARS.                                      |
| NOFEARS                                     | Modify NOTEARS so that the scoring function remains convex to ensure local minima.                                                                                                                          |
| GAE                                         | Scalable graph autoencoder framework (GAE) whose training time increases linearly with the number of variable nodes.                                                                                           |
| GRAN-DAG                                    | Extends the NOTEARS algorithm for non-linear relationships.                                                                                                                                                  |
| CGNN (Causal Generative Neural Network)     | Generative model of the joint distribution of the variables reducing the maximum mean discrepancy (MMD) between graph and data.                                                                            |
| SAM (Structural Agnostic Modeling)          | Structurally agnostic model for causal discovery and penalized adversarial learning.                                                                                                                        |
2.1 Constraint-based methods

Among the most common constrained-based algorithms are PC and its variants, and the fast causal inference (FCI) algorithm.

2.1.1 PC and its variants

The PC algorithm was proposed by Peter Spirtes and Clark Glymour and named after them [10]. In this algorithm, a completed partially directed acyclic graph (CPDAG) is produced by iteratively checking the conditional independence relations of two adjacent nodes conditioned on all-size subsets of their neighbors. Three assumptions underlie the algorithm: no confounder variable, the causal Markov condition, and faithfulness. Under these conditions, this algorithm generates a partially directed causal graph that is proved to be asymptotically correct.

The PC algorithm is order-dependent, i.e., the output of the algorithm can depend on the order in which variables are provided to the algorithm. To address this problem, Colombo and Maathuis [11] developed the PC-stable algorithm, in which the deletion of an edge takes place at the end of each stage (taking into account any two nodes’ relations within a predetermined neighborhood). Thus, any ordering of vertices will result in the same edge deletions, resulting in the same stable output.

The PCMCI [11,12] and PCMI+ [11–13] are two extensions of the PC algorithm proposed to handle large-scale time-series datasets. In this concept, a temporal variable $X_t$ is treated as multiple variables at different points in time. The PCMCI algorithm consists of two stages: (1) the PC stage tries to identify a superset of parents $\hat{p}(X_i^j)$ for all time series variables $X_i^j \in \{X_1^t, \ldots, X_N^t\}$, the purpose is to reduce dimension by removing the irrelevant conditional variables, and (2) the momentary conditional independence (MCI) test to test whether $X_{t-\tau}^j \rightarrow X_t^j$ with conditional independence test $X_{t-\tau}^i \perp X_{t-\tau}^j | \hat{p}(X_i^j \setminus \{X_{t-\tau}^i\}), \hat{p}(X_{t-\tau}^i)$. The $\hat{p}(X_i^j) \subset X_t^j = (X_{t-1}^j, X_{t-2}^j, \ldots)$ denotes the causal parents of variable $X_t^j$ among the past of all $N$ random variables. The PCMI+ algorithm consists of four stages: the first step identifies a superset of lagged parents $\hat{B}_t^\sim(X_i^j)$ and in the second phase, performs tests $X_t^i \perp X_t^j | S, \hat{B}_t^\sim(X_i^j), \hat{B}_t^\sim(X_t^i | X_{t-\tau}^i)$ where the $\hat{B}_t^\sim(X_i^j)$ contains all lagged parents of all contemporaneous ancestors of $X_t^j$. In the 3rd and 4th stages, it adopts the PC algorithm’s orientation rules to orient the edges.
2.2.2 Inductive Causation (IC) algorithm and its variants

The IC algorithm takes the estimated probability distribution of random variables with an underlying DAG structure and outputs the equivalent class of the DAG \[14,15\]. PC, in contrast, provides a schematic search method and is thus considered a refinement of IC.

The IC* algorithm \[15,16\] is an extension of the IC algorithm that searches for causal relations using observations of a set of variables, even when they appear as latent variables. The output of the IC algorithm is a CPDAG which only has directed edges (identified causation) and undirected edges (undetermined causation). The output of the IC* algorithm is an embedded pattern, i.e., a hybrid graph containing two more types of edges. A dashed arrow edge (a\rightarrow b) indicates a potential causal relationship, which could either reflect a true causal relationship (a\rightarrow b) or the presence of a latent variable z (a\leftarrow z\rightarrow b). The bidirectional arrow edge (a\leftrightarrow b) indicates that there is certainly a latent variable z between them (a\leftarrow z\rightarrow b). The IC* algorithm and the IC algorithm differ when inferring edge direction (Appendix, steps 2 and 3).

2.2.3 Fast Causal Inference (FCI) and its extensions

FCI (fast causal inference) is a modification of the PC algorithm \[15,17\] that detects unknown confounding variables and produces asymptotically correct results. FCI improves on the PC algorithm by adopting two rounds of the phases of the PC algorithm. The algorithm first uses PC-phase I to find an initial skeleton, then uses the separation set to orient all v-structures triples and outputs a CPDAG; then performs another round of skeleton searching based on the CPDAG, and repeats the orientation for unshielded triples.

The really fast causal inference (RFCI) algorithm \[18\] skips the second step, which is the most time-consuming part of the task, and therefore significantly speeds up the FCI procedure. A set of 10 rules is added to the algorithm to orient the skeleton's edges. The detailed steps of FCI and RCFI algorithms can be found in \[19\] and its supplementary materials.

2.3 Score-based methods

In addition to the traditional combinatorial methods discussed above, score-based methods have also been used to uncover causal structure. Score-based methods include the Greedy Equivalence Search (GES) algorithm, the fast GES algorithm, and the K2 algorithm.

2.3.1 GES algorithm

The GES algorithm was proposed by Chickering \[20\], and its underlying principles are from Meek \[20,21\]. The algorithm starts with an empty graph and iteratively adds and deletes edges in the graph by optimizing a score function. During the forward phase, the algorithm searches iteratively from the space of DAGs created by one edge addition on the current DAG and selects the edge with the best score. The forward phase ends when the score is no longer increasing. In the second phase, the algorithm repeats the above step, but deletes one edge at a time, and selects the edge that improves the score the most. The algorithm stops as soon as there are no more edges to be deleted.

The score function should be decomposable, meaning that the score of the entire graph is the sum of the individual (logged) scores of each node given its ancestors. A typical score function is the BIC score. The GES algorithm uses different score functions for different data types:
Bayesian information criterion (BIC) score (for continuous data), likelihood-equivalence Bayesian Dirichlet uniform joint distribution (BDeu) score (for discrete data), and Conditional Gaussian score (for continuous/discrete mixture data).

\[ \text{BIC} = k \ln(n) - 2 \ln(\hat{L}) \]

where \( \hat{L} \) is the maximized likelihood function of the model, \( n \) is the observational data and \( k \) is the degree of freedom. For the definition of the BDeu scoring function, please refer to Buntine [20–22]. The Conditional Gaussian score is defined on the ratios of joint distributions, Andres et al. has proved that the Conditional Gaussian score is score equivalent [23], i.e., a scoring function that scores all DAGs in the same MEC equally.

### 2.3.2 Fast GES (FGES)

FGES is an improved and parallelized version of GES. A significant speedup is achieved by storing the score information in the course of the GES algorithm [24]. In addition, several insights regarding parallelization were offered in the paper. First, the precalculation of covariances can be parallelized by variables. Secondly, it is possible to parallelize the process of calculating edge scores when an edge addition is being performed on the graph. In particular, a greater speed-up can be achieved for sparser graphs.

### 2.3.3 K2 Algorithm

The main idea of the K2 algorithm [25] is to perform a greedy heuristic search for the parents of each node. For each node, the algorithm iteratively decides the parents. When visiting node \( X_i \), the algorithm searches for all possible parents of \( X_i \) (\( X_j \) such that \( j \) has a lower ordering of \( i \)). The algorithm greedily adds \( X_j \) to the parent set of \( X_i \) if it could increase a pre-defined score function. The iteration for the node \( X_i \) stops when the parent node’s number reaches the (preset) maximum, or adding an \( X_j \) does not increase the score anymore. The entire algorithm finishes after finishing iteration for all \( X_i \).

### 2.4 Hybrid Algorithms

#### 2.4.1 Max-Min Hill Climbing (MMHC) algorithm

The Max-Min Climbing algorithm is a combination of the constraint-based algorithm and score-based algorithm [26]. It uses the Max-Min Parents and children (MMPC) (A detailed description was provided in [26,27]) to find the skeleton of the Bayesian network and then performs the constrained greedy search to orient the edges.

In the finding skeleton stage, the algorithm repeats two phases (forward and backward) for each variable \( X_i \). In the forward phase, the algorithm sets the candidate parents and children (CPC) of variable \( X_i \) to an empty set and performs the MaxMinHeuristic search algorithm, which is the key part of the MMHC algorithm and also the name 'Max-min' comes from. It searches for all
variables $X_j \in V \setminus \{X_i, CPC\}$ and selects the $X_j$ that maximizes the minimum association $\text{MinAssoc}(X_j, X_i | CPC)$ (the estimation of the association strength of $X_i$ and $X_j$ given CPC) to add to the set CPC. The forward phase stops when the set CPC does not change anymore. In the backward phase, the algorithm searches for all $X_j$ in the set CPC and all subsets $S$ of CPC, if it finds a conditional independence relationship $\text{Ind}(X_j, X_i | S)$, then the variable $X_j$ is removed from the set CPC.

In the second orientation stage, the MMHC algorithm first decides the score to use (e.g. BDeu scoring function). The MMHC starts with an empty graph and performs the Greedy Hill-Climbing with edge-adding, edge-deletion, edge-reversion, and only tries adding edge $Y \rightarrow X$ if $Y \in CPC_{X_i}^2$.

2.5 Algorithms for Functional Causal Models (FCMs)

2.5.1 LiNGAM

The LiNGAM model was originally proposed by Shimizu [28] to learn linear non-Gaussian acyclic causal graphs from continuous-valued data. The LiNGAM transfer the linear structure model $x_i = \sum_{j<i} b_{ij} x_j + e_j$ to the form of $x = Bx + e$, and the causal structure problem becomes an optimization problem for matrix $B$. There are several extensions of the LiNGAM model by using different estimation methods, including the ICA-based LiNGAM [28,29], the DirectLiNGAM [30], and the Pairwise LiNGAM [31].

2.5.2 Additive Noise Models

The non-linear additive noise model was proposed by [31,32]. The model assumes the observed data is generated according to the following model:

$$x_i = f_i(x_{pa(i)}) + n_i.$$

Here $f_i$ is an arbitrary function, $x_{pa(i)}$ denotes the ancestor nodes of node $x_i$ in the true causal graph, and $n_i$ is the noise variable of an arbitrary probability density function. The paper proves the basic identifiability principle for the two variables case and generalizes their results to multiple variables.

3. Causal Structure Discovery: Continuous Space Algorithms

The traditional discovery algorithms try to discover a causal graph (which is usually a directed acyclic graph (DAG) while searching for the optimal graph in the space of candidate graphs).

The traditional combinatorial optimization problem of DAG learning is given by
\[
\min_{A \in \mathbb{R}^{d \times d}} F(A) \text{ where } G(A) \in \Delta
\]

Here \(\Delta\) is the set of all DAGs with \(d\) nodes, and \(F(A)\) is the cost/score function.

The problem of searching all DAGs is usually intractable, and super-exponential in the number of nodes in the graph. An alternative approach would be to model the problem as a continuous space optimization problem, which would then allow various learning techniques to be applied. Recently, a number of publications have explored continuous optimization methods that learn directed acyclic graphs (DAGs) by adding a acyclicity constraint. In these approaches, the discrete acyclicity constraint \(G(A) \in \Delta\) is replaced by \(h(A) = 0\), where \(h(A)\) is a smooth function that ensures the acyclicity of \(G(A)\).

In other words, the hard constraints on acyclicity can be relaxed and it can be incorporated into the loss function to be optimized. This smooth continuous constraint allows the use of machine learning-based tools, which in turn can make the algorithms scalable in the presence of large amounts of data.

### 3.1 NOTEARS algorithm

The NOTEARS algorithm [33] considers the acyclicity constraint and comes up with a smooth function \(h(A)\), whose value characterizes the “DAG-ness” of the graph with adjacency matrix \(A\).

\[
h(A) = \text{Trace}[\exp(A \odot A)] - d
\]

\(h(A)\) equals zero if and only if \(G(A)\) is acyclic, and more severe deviations from acyclicity would increase the value of the function. Its derivatives are easier to compute, which makes it easier to optimize \(A\), although the constraint \(h(A) = 0\) is nonconvex. This paper assumes a linear SEM model

\[
X_i = A^T X_i + Z_i,
\]

where \(X_i\) is a \(d\)-dimensional sample vector of the joint distribution of \(d\) variables and \(Z_i\) is a \(d\)-dimensional noise vector. We denote \(n\) such samples by the matrix \(X\), and the loss function (with \(l_1\)-regularization) is given by

\[
F(X, W) = \frac{1}{2n} \| X - AX \|_F^2 + \lambda \| A \|_1.
\]

The paper on learning sparse nonparametric DAGs is an extension of NOTEARS, which tries to define a “surrogate” of the matrix \(A\) above for general nonparametric models to optimize the loss functions. [34].
3.2 NOBEARS algorithm

Several other improvements like the NOBEARS algorithm improve the scalability of the NOTEARS algorithm[35]. A fast approximation of a new constraint is proposed, as well as a polynomial regression loss model to account for non-linearity in gene expression to infer gene regulatory networks.

3.3 DAG-GNN: Graph-based Neural Network

A DAG-GNN generalizes the above NOTEARS algorithm by considering non-linearity in SEMs [36]. It can be modeled with a variational autoencoder neural network with a special structure with an encoder $Z = g_1((I - A^T)^{-1} g_2(X))$, and a decoder $X = f_2((I - A^T)^{-1} f_1(Z))$ and where $g_1, g_2$ are parameterized functions which can be assumed to serve as the inverse of $f_1, f_2$ respectively.

This variational framework considers $Z$ to be a latent vector (instead of considering it the noise in linear SEM), which can have a dimension other than $d$. However, if $d$ is low, one can consider smaller dimensions of $Z$. The decoder then tries to reconstruct the data from this latent variable.

The encoder and decoder can be trained together from $n$ samples of $X, (X_1, X_2, ..., X_n)$ such that the loss function

$$F(X, A, \theta) = \frac{1}{n} \sum_{k=1}^{n} [\log p(X_k | Z)] - KLD(q(Z | X_k) | \parallel p(Z))$$

is minimized. The constraint in this optimization process to ensure the acyclicity of the matrix $A$ is slightly modified to

$$h(A) = Tr[(I_d + \alpha A \circ A)^d] - d = 0$$

where $\alpha$ is an arbitrary parameter. In GPU-based deep learning libraries, this constraint can be implemented more easily, making the algorithm highly scalable.

3.4 NOFEARS

Wei et al. show that the NOTEARS algorithm fails to satisfy the Karush-Kuhn-Tucker (KKT) regularity conditions[37]. They, therefore, reformulate the problem to ensure that the convexity of the scoring function can still ensure local minima, even when the constraints are non-convex. This new algorithm, called the NOFEARS algorithm, has the following acyclicity constraint.

$$h(A) = \sum_{p=1}^{d} c_p Tr[A^p] = 0$$

3.5 Graph AutoEncoder (GAE)

Ng et al. propose another graph autoencoder framework (GAE) for causal structure learning [38], which improves the training time as well as performance over DAG-GNN for both linear and nonlinear synthetic datasets.
3.6 GRADient-Based Neural DAG (GRAN-DAG)

Similarly, GRADient-Based Neural DAG Learning extends the NOTEARS algorithm to include non-linear relationships between variables[39]. It uses a fully connected network of \( L \) layers for each of the \( d \) variables. The input for the network for variable \( j \) is \( X_{-j} \), which masks the \( j \)-th position of the sample \( X_j \) to 0, and the output is the parameter vector of the desired distribution for that variable \( \hat{X}_j \).

3.7 Causal Generative Neural Network (CGNN)

Goudet et al. proposed a causal generative neural network (CGNN) which learns a generative model of the joint distribution of the variables by reducing the maximum mean discrepancy (MMD) between the real data and generated data. The learned graph is then adjusted to remove cycles. They also extend it to include the case of latent variables or confounders[40].

3.8 Structural Agnostic Model (SAM)

Another algorithm proposes a structurally agnostic model (SAM)[41] for causal discovery and penalized adversarial learning, where the input is also \( X_{-j} \), but the output is the estimate \( \hat{X}_j \). Thus this method improves upon the complexity of the CGNN algorithm.

3.9 Reinforcement learning-based methods

Reinforcement learning-based methods (RL-BIC) have been discovered recently that consider both the acyclicity constraint and the Bayesian Information Criterion (BIC) score in the reward function and attempt to learn the DAG[42]. They use an actor-critic model, where the actor is an encoder-decoder framework which takes in data as input and outputs the graph. The critic takes the reward function for this graph and updates the proposed graph.

4 Performance comparison

This section provides results to compare the effectiveness of some causal structure learning algorithms on synthetic data. The synthetic data is generated in the same way as the DAG-GNN paper. An Erdos-Renyi model with an expected node degree of 3 is used to generate the random graph, and the adjacency matrix is formed by assigning weights to the edges from a uniform distribution. The sample is generated by using the following structural equation:

\[
X = g(A, Z, X)
\]

Where \( Z \) is random Gaussian noise. We consider two functions for \( g(X) \). The first is the (linear) identity function \( g(A, Z, X) = A^T X + Z \), and the second is the nonlinear function \( g(A, Z, X) = A^T \cos(X + 1) + Z \).
We evaluated six algorithms, PC, GES, GFCI, MMHC, DAG-GNN, and GAE on four metrics, Structural Hamming Distance (SHD↑), True Positive Rate (TPR↑), False Positive Rate (FPR↓), and False Discovery Rate (FDR↓), and show their results in Fig. 2. In all these evaluations, we consider any bidirectional edges as half discovered. In experiments (a)-(d), the data is drawn from a distribution according to the underlying causal graph where relationships between nodes are linear, and (e)-(h) are non-linear. In all experiments, the number of nodes of the graph ranges from 10, 20, 50, and 100. For each graph size, we draw 5 different datasets from the graph structure with sample size N=1000, and calculate the four evaluation metrics and take the average. We also evaluated these algorithms on the Sachs dataset[9] on the above four metrics, and show their results in Table 2.

| Metric | PC   | GES  | GFCI | MMHC | DAG-GNN | GAE |
|--------|------|------|------|------|---------|-----|
| SHD    | 24.5 | 26.5 | 29.5 | 22   | 19      | 22  |
| FDR    | 0.77 | 0.72 | 0.79 | 0.68 | 0.71    | 0.89|
| TPR    | 0.32 | 0.56 | 0.44 | 0.47 | 0.11    | 0.05|
| FPR    | 0.49 | 0.64 | 0.72 | 0.45 | 0.13    | 0.21|

Table 2: We evaluated six algorithms, PC, GES, GFCI, MMHC, DAG-GNN, and GAE on four metrics, Structural Hamming Distance (SHD), True Positive Rate (TPR), False Positive Rate (FPR), and False Discovery Rate (FDR) for the Sachs dataset[9], and show their results in Fig. 2. In all these evaluations, we consider any edge whose direction is reversed as half discovered.
6. Application to Biomedicine

Traditional methods such as the PC algorithm have been used to deduce phenotype network structure and genetic architecture jointly[43]. A gene regulatory network[1] is one example of a causal structure that can be used to develop interventions to control gene expression. It uses a method called Difference Causal Inference (DCI) and compares it to a difference-based GES as a baseline. Another work proposes a hybrid algorithm which combines Simulated Annealing with Greedy Algorithm (SAGA) to predict inter-gene transcriptional regulatory relationships. As big data, such as data from cell types and disease states, becomes more common, such algorithms will become even more relevant.

Apart from gene regulatory networks, there are also networks like those represented in the Sachs dataset[9], which incorporates measurements of 11 phosphorylated proteins and phospholipids simultaneously. In our comparative analysis of the performance of this dataset, we find that machine learning models can also be effective at determining causal structure.

Research into the brain connectivity patterns between components of neuronal networks is another exciting area of research[44]. By functional magnetic resonance imaging (fMRI), neuronal activity has been associated with cognitive function and behavioral traits. The hierarchical networks learned in this area have used Bayesian Nets based algorithms like PC, GES, FCI, etc. and data-driven approaches like LiNGAM. In some cases, machine learning-based approaches may be worthwhile to explore because of their natural robustness to some noise in the data. In our review, we limit ourselves to methods which learn DAG structure from data.

Thus, there is a need to develop newer techniques for causal discovery, for which new machine learning algorithms promise to be worth exploring, notably in approaches where directed graphs can be used to define stronger causal relations. It may also be necessary to change the mathematical formulations for the desired causal structure by implementing new constraints or reducing constraints in existing algorithms. Machine learning models, under sufficient data, can be robust to certain discrepancies like sample bias, missing data, erroneous measurements. Many of these applications have, in fact, also focused on weaker concepts of causality, such as pairwise directionality, during the analysis of gene networks[45] and brain connectivity networks[46].

5 Discussion

It is clear from the results that different algorithms have different advantages and disadvantages. While the PC algorithm performs well across both linear and nonlinear data, it has low TPR and is computationally intensive. The GES, GFCI, and MMHC algorithms show a very high FPR, but their TPR is higher than that of the PC algorithm.

The continuous constraint-based algorithms generally show a very low false discovery rate (FDR), except for the benchmark Sachs dataset. This is generally due to the fact that both linear and non-linear models are based on structural equation models (SEMs) with the same causal relationship function at every node, which is what these algorithms assume when they learn the
causal structure, but one cannot guarantee the same for Sachs data because such constraints cannot be defined \textit{apriori}. This is corroborated by recent results from Zhu et al.\cite{42} where such gradient-based methods perform poorly on data generated by a nonlinear model where every causal relationship (node function) is sampled from a Gaussian distribution. However, this is a growing area of research.

These machine learning models are more scalable and might be useful in the era of big data. Traditional methods might have complexities which grow exponentially with the number of attributes. In spite of the nonconvexity of the optimization proposed by Zheng et al. \cite{33}, optimization and learning strategies can be employed to help find the optimal solution. A few methods have been used to solve this problem using augmented Lagrangian approaches\cite{36,38}. The NOBEARS algorithm reduced the computing complexity of NOTEARS from cubic to quadratic in number of attributes\cite{35}, allowing for smooth implementation in datasets which have more than 4000 attributes. The algorithms are also highly parallelizable, and most of the algorithms use deep learning libraries such as Tensorflow\cite{47} and PyTorch\cite{48}.

6 Conclusion

Causal structure learning has been studied for a long time and is an NP-hard problem. Various traditional approaches have been studied to tackle this problem, the most important among these being the PC algorithm. This was followed by literature on score-based methods, which are computationally faster. Because of the continuous constraint on acyclicity, there are new deep learning approaches to the problem in addition to traditional and score-based methods. Such methods can also offer scalability, especially when there is a large amount of data involving multiple variables. Utilizing our own evaluation metrics and experiments on linear, non-linear, and benchmark Sachs data, we aim to highlight the various advantages and disadvantages associated with these methods for the healthcare community.

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**Tools**

| Method                                      | R-package                  |
|---------------------------------------------|-----------------------------|
| PC (named after Peter Spirtes and Clark Glymour) | R-pcalg, R-bnlean, Tetrad, Python-pgmpy |
| IC (Inductive Causation)                    | Python-causality            |
| FCI (Fast Causal Inference)                 | R-pcalg, Tetrad             |
| GES (Greedy Equivalence Search)             | R-pcalg, Tetrad             |
| Fast GES                                    | Tetrad                      |
| K2                                          | [github.com/ruteee/K2-Algorithm](https://github.com/ruteee/K2-Algorithm) |
| Max-Min Hill Climbing (MMHC)                | R-mmhc, Python-pgmpy, R-bnlean |
| LiNGAM (Linear Non-Gaussian Acyclic Model)  | R-pcalg, Tetrad             |
| GRAN-DAG                                    | [github.com/kurowasan/GraN-DAG](https://github.com/kurowasan/GraN-DAG) |
| DAG-GNN                                     | [github.com/fishmoon1234/DAG-GNN](https://github.com/fishmoon1234/DAG-GNN) |
| NOTEARS                                     | [github.com/xunzheng/notears](https://github.com/xunzheng/notears) [github.com/skypea/DAG_No_Fear](https://github.com/skypea/DAG_No_Fear) |
| Method  | Repository                                      |
|---------|-------------------------------------------------|
| GAE     | github.com/huawei-noah/trustworthyAI/tree/master/Causal_Structure_Learning/GAE_Causal_Structure_Learning |
| RL-BIC  | github.com/huawei-noah/trustworthyAI/tree/master/Causal_Structure_Learning/Causal_Discovery_RL     |
| SAM     | github.com/Diviyan-Kalainathan/SAM               |
| CGNN    | github.com/GoudetOlivier/CGNN                   |