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Restricted-derestricted dynamic Bayesian Network inference of transcriptional regulatory relationships among genes in cancer

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ABSTRACT

Understanding transcriptional regulatory relationships among genes is important for gaining etiological insights into diseases such as cancer. To this end, high-throughput biological data have been generated through advancements in a variety of technologies. These rely on computational approaches to discover underlying structures in such data. Among these computational approaches, Bayesian networks (BNs) stand out because their probabilistic nature enables them to manage randomness in the dynamics of gene regulation and experimental data. Feedback loops inherent in networks of regulatory relationships are more tractable when enhancements to BNs are applied to them. Here, we propose Restricted-Derestricted dynamic BNs with a novel search technique, *Restricted-Derestricted Greedy Method,* for such tasks. This approach relies on the *Restricted-Derestricted Greedy search technique* to infer transcriptional regulatory networks in two phases: restricted inference and derestricted inference. An application of this approach to real data sets reveals it performs favourably well compared to other existing well performing dynamic BN approaches in terms of recovering true relationships among genes. In addition, it provides a balance between searching for optimal networks and keeping biologically relevant regulatory interactions among variables.

1. Introduction

Identification of functional causes and contributing mechanisms of disease is a pre-eminent aim in biomedical research. Cancer, like other diseases associated with organs, is not completely understood as it is characterized by complex genetic changes involving multiple mutated genes. Thus, interactions among genes (or gene products) can lead to insights into the etiology of diseases. Transcriptional regulatory networks serve this purpose by specifying relationships for identifying regulator gene and target gene interactions. Particularly, with the abundance of gene expression data due to the invention of DNA microarray and next-generation sequencing technologies, several computational approaches have been developed for reverse-engineering regulatory networks of genes.

In recent times, these approaches have become useful for modelling cellular networks, protein signalling pathways and genetic data analysis (Friedman, 2004; Sachs et al., 2005; Beaumont and Rannala, 2004). Particularly, while a deterministic approach models a system of ordinary differential equations (ODE) (Gardner et al., 2003; Greenfield et al., 2010), information-theoretic approaches based on mutual information (MI) infer relationships after comparing MI measures with a putative threshold (Stuer et al., 2002; Butte AJ Kohane, 2000). In order to reduce false predictions by these methods, algorithms such as the Context Likelihood of Relatedness (CLR), Algorithm for the Reconstruction of Accurate Cellular Networks (ARACNe) and Minimum Redundancy Network (MRNET) adjust MI measures and distinguish between direct and indirect interaction networks (Faith et al., 2007; Margolin et al., 2006; Meyer et al., 2007). Furthermore, probabilistic graphical models infer undirected networks (in Gaussian graphical models) (Ambroise et al., 2009) and directed networks (in Bayesian Networks) under causal Markov assumptions (Friedman et al., 2000; Needham et al., 2007). In addition to directed nature of the Bayesian Networks (BNs), the probabilistic nature handles the process of gene regulation and the noise inherent in microarray measurements and the graphical outlook conveys linear and higher order dependencies between genes, which are easily interpretable. These make them useful for inference of transcriptional regulatory relationships among genes.

With regards to inference from the time-course data, ODE (Bansal et al., 2007) and logic (Morris et al., 2010) –based models constrain numbers of variables in networks although this is circumvented in methods such as Relevance networks and Markov Random networks (Kim et al., 2013; Remondini et al., 2005; Song et al., 2009). BNs are

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extended to dynamic BNs (DBNs) where variables are indexed by time and the regulatory relationships are governed by a Markov process in such cases (Needham et al., 2007). These incorporate temporary invariant networks. However, due to the exponential rise in the search space of networks, as the number of variables increases, heuristic methods are employed to search for optimal networks. For this reason, even though networks may be highly rated by DBN methods, sometimes they lack the quality most desirable of inferred regulatory networks, i.e. recovering true regulatory relationships among genes. On the other hand, non-homogeneous dynamic Bayesian networks have been recently applied to infer gene regulatory networks. Although some of these methods are useful in contexts where networks at each time undergo systematic changes, others have been based on time varying parameters (Ahmed and Xing, 2009; Lèbre et al., 2010; Grzegorczyk and D, 2013; Dondelinger and Husmeier, 2013).

1.1. Some heuristic search methods

Heuristic methods such as the Hill-Climbing (Greedy) (Chickering, 1996) and Simulated Annealing (Heckerman, 1995; Janzura and Nielson, 2006) are among the most widely used strategies for learning BN structures. Advancements to the Greedy method involve repeating the method several times with different initial solutions (Chickering, 1996). This is known to provide a more thorough search for near optimal solutions of search problems. While Greedy methods are prone to convergence on local optimal solutions, Simulated Annealing search techniques are able to escape local optima traps in some cases, as they employ an annealing technique to accept new solutions. Also, hybrid methods have been employed. These include the Max–Min Hill Climbing hybrid algorithm, which infers a skeleton of Bayesian Network with the constraint-based approach (Tsamardinos et al., 2006), and combinations of Greedy and Simulated Annealing methods (Wang et al., 2007; Adabor et al., 2015).

Besides population-based search methods such as the Ant Colony Optimization, the Particle Swarm optimization, and the Genetic Algorithm (GA) have also been applied to learning BN structures as they outperform some sequential search methods (Daly and Shen, 2009; Cowie et al., 2007). GA approaches are distinguished through selection of subsets of fitter solution candidates as parents to produce new solutions, using evolution operators. New solutions are compared with previous populations of solutions to select the fittest solutions for subsequent steps of the method (Larrañaga et al., 2013; Larranaga et al., 1996a,b). These population-based approaches, usually starting without prior networks, are very useful when there is no idea about expected final network solutions because they are very expensive, requiring the evaluation of each member of the population at each step of iteration to ascertain suitable members for subsequent operations (Sivanandam and Deepa, 2008). However, in this study, we infer transcriptional regulatory relationships among genes using prior networks derived from domain knowledge to guide the methods to realistic predicted networks.

1.2. Proposed compound approach

In order to achieve networks that meet true recoveries, we present an approach to reverse-engineer DBNs of transcriptional regulatory relationships among genes from gene expression profiles. This approach involves a two-phase inference: first, a preliminary inference which applies a new modified greedy method with random restarts by limiting the number of parents of target genes to only one regulator gene, and then later allowing every relationship to be explored in a greedy search with random restarts in the final phase. The preliminary phase has the advantage of exploring the principal parents of each target gene, hence enhancing the quality of inferred relationships in the regulatory networks. In addition, with random restarts during inference, our approach guarantees near optimal networks (solutions) within search spaces. Thus, it escapes from being trapped on local optimal networks, which are undesirable for search problems. It must be stressed that the novelty of this approach lies in the concatenating implementation of the modified variants of the Greedy search techniques.

2. Materials and methods

2.1. Bayesian network

BNs are probabilistic graphical models that describe the joint probability over a set of variables. To reverse-engineer transcriptional regulatory networks, the BNs encode joint distributions of the set of measured gene expressions such that while the variables represent regulator and target genes, edges represent the regulatory relationships between transcription factors and target genes. In other words, the dependencies between the variables of a BN denote the regulatory interactions among genes of interest. For instance, if a BN has an edge directed from a source *CTP2* to a target, *GATA6*, then the model predicts that a transcription factor *CTP2* regulates its target gene, *GATA6*. Under such circumstance, *CTP2* is said to be the parent of *GATA6*.

More formally, for a set of random variables $X = \{X, ..., X_n\}$, a BN is defined as a pair (G, P), where G represents a directed acyclic graph (DAG) on X and P is a joint probability distribution on X. In order to represent causal relationships between variables, this definition requires the causal Markov condition to be satisfied: each variable is independent of every other variable conditional on all its causes (Bansal et al., 2007). Using the chain rule of probability and the Markov assumption, it can readily be shown that the joint probability distribution over the set of variables is

$$(X_1, X_2, ..., X_n) = \prod_{i=1}^{n} P\langle (X_i) | Pa(X_i)), \tag{1}$$

where $Pa(X_i)$ denotes the set of parents of variable X_i.

2.2. BN inference problem

The problem of inferring BN structures is to find a network, G, that best fits a given dataset, D, such that G is in the space of DAGs. Algorithms for constructing BN structures have two major components: a scoring metric, and a searcher that searches for networks. The scoring metrics build on Bayes' Theorem to compute the posterior probabilities of network structures from the dataset to evaluate networks. The posterior can be expressed as:

$$P(G\ |D) = \frac{P(D\ |G)P(G)}{P(D)}, \tag{2}$$

where $P(D\ |G)$ is the marginal likelihood of the data given the network, G, and $P(G)$ is the prior probability of the network structure. Usually, a proportional relation between the posterior and the numerator of Eq. (2) is explored in scoring networks since $P(D)$ is independent of networks. Thus, they are not required to compare networks. The Bayesian scoring metric can be generally described as

$$Score(G{:}\ D) = \log P(G|D) = \log P(D|G) + \log P(G) - \log P(D), \tag{3}$$

and the marginal likelihood that averages the probability of data over all possible parameters in G is expressed as:

$$P(D|\ G) = \int P(D\ |G, Q)P(Q\ |G)dQ \tag{4}$$

Various Bayesian scores that have been proposed are distinguished by the choice of the priors $P(G)$ and $P(Q\ |G)$ for each G (Friedman et al., 2000). However, in order to avoid over-fitting the models due to the high numbers of parameters that occur in practice, we use the Bayesian Dirichlet equivalence metric (BDe) to evaluate networks (Heckerman et al., 1995; Cooper and Herskovits, 1992). In addition, the BDe is useful because it discriminates between simple and complex structures,

just like Occam's Razor at work. This is achieved as it assumes a Dirichlet prior distribution for the priors over parameters $P(Q|G)$ and a uniform prior $P(G)$ which incorporates a penalty function (Adabor et al., 2015). In principle, it assumes the likelihood equivalence property which implies that the scores of two isomorphic networks are equal (score equivalence).

Each network is evaluated by the score metric. Sample networks are generated through searching neighbours of the most recent network. This is searched within the space of all possible DAGs that fit the data set. Although Robinson (Robinson (1977)) presents a function to determine the number of such DAGs for a given number of nodes, searching through all possible networks is an NP-hard problem (Chickering, 1996). Therefore BNs rely heavily on heuristic methods (See (Adabor et al., 2015)). Generally, heuristic methods conduct any of the following at any iteration: an existing edge between variables can be reversed or deleted, or new edges may be introduced to connect variables that were not connected previously while ensuring that the resulting network is acyclic. For example, for a transcription regulatory relationship network involving two variables, X_1 and X_2, an outcome could be "X_1 regulates X_2", "X_1 is regulated by X_2", or simply, "there is no edge (interaction) between X_1 and X_2".

2.3. Restricted-derestricted dynamic Bayesian network

It is worthy of note that biological systems also involve feedback loops which make the cyclic requirements of (static) BNs inapplicable. Therefore an extension of BN, the Dynamic Bayesian networks (DBN) (Friedman et al., 1998) are used to model time series and data that incorporate feedback loops. In the modelling of DBN, the gene expression values at a given time, t, is inferred from the expression value of the gene and its parents at the previous time, $(t-1)$. Thus, the variables depend only on information at the previous time step (Fig. 1). This is the first order Markov assumption. Here, the variables have Markov lag one. Also, the DBNs do not imply the networks change over time because they assume stationarity of the models. In this way, BNs are extended to incorporate time and feedback loops of the transcriptional regulatory relationships among genes. However, for efficient inference of transcriptional regulatory relationships among genes, we introduce a search method called *Restricted-Derestricted Greedy Method*, for use in inferring the DBNs from gene expression profiles. DBNs inferred in this way are here called *Restricted-Derestricted DBNs*.

This method, which searches for networks in greedy ways by only retaining best-scoring networks, involves two phases: phase 1 (restricted inference), and phase 2 (derestricted inference). In the preliminary phase 1, it infers gene regulators (parents) while restricting the number of parents (other than variable's previous state) to any variable (target) to one at the Markov lag one, and then removes this restriction in the final phase 2.

More specifically, the *Restricted-Derestricted Greedy Method* for searching for networks is a sequentially combined implementation of restricted greedy searches and derestricted greedy searches. It commences with an initialization of a prior network, continues with the generation and evaluation of new networks in different stages until a stopping condition is met. As long as the condition for termination of the entire process of search for optimal networks (based on scores) is not met, the inference procedure repeats itself (Fig. 2).

2.3.1. Stopping conditions

The search method at any of the phases of the method could be terminated by a predetermined number of networks to be searched, predetermined number of restarts of the search, or after a desired duration (time) of search. When any of the specified stopping criteria for the preliminary restricted phase is met, the method proceeds to the next (derestricting) phase. The method terminates when the criterion for stopping at the final phase is satisfied.

The approach in the preliminary phase permits most critical regulators to be explored, which is consistent with transcription factor-gene interactions. Also, it provides a more guided search to find networks with high BDe values as well as valid relationships between variables which are consistent with actual transcriptional regulatory relationships. This is because most regulator-target gene pairs are identified in the restricted phase, only to prune inference volume in the final phase. In addition, the approach allows random restarts during both phases of the search to escape being trapped in local optimal networks. A constraint to the implementation of the method is the availability of the computer memory required to solve problems involving large numbers of variables and samples or observations. In general, the higher the numbers of variables and samples in the data, the higher the memory that may be required. In addition, with regards to amount of computations, the edge connecting any pair of variables or nodes can be reversed or removed, and in case there is no edge between the pair of variables, an edge can be introduced to link the variables in the search process at each stage. This implies that for n variables, there are $O(n^2)$ possible changes. This is similar to other search methods implementing similar strategies. An application to reverse-engineering the transcriptional regulatory relationships in breast cancer revealed that it compares well with existing best performing methods applicable to the problem.

2.4. Materials and datasets

In order to test methods for inference in breast cancer, we used four relevant gene expression data sets obtained from the Gene Expression Omnibus (GDS4088, GSE40066 and GSE4917) and The Cancer Genome Atlas (TCGA). In all, GDS4088 (GDS4088 data) comprised of 623 genes and 86 arrays (Supplementary Table S1) while GSE40066 (GSE40066

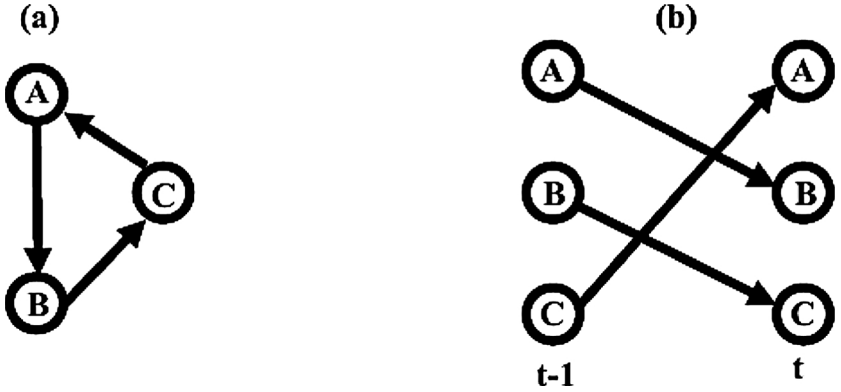

Fig. 1. Dynamic Bayesian network. (a) A network with loop. (b) Dynamic Bayesian network explicitly denoting time. Network (b) is an alternative representation of network (a). State of variables at time t depends only on the information at time, t-1.

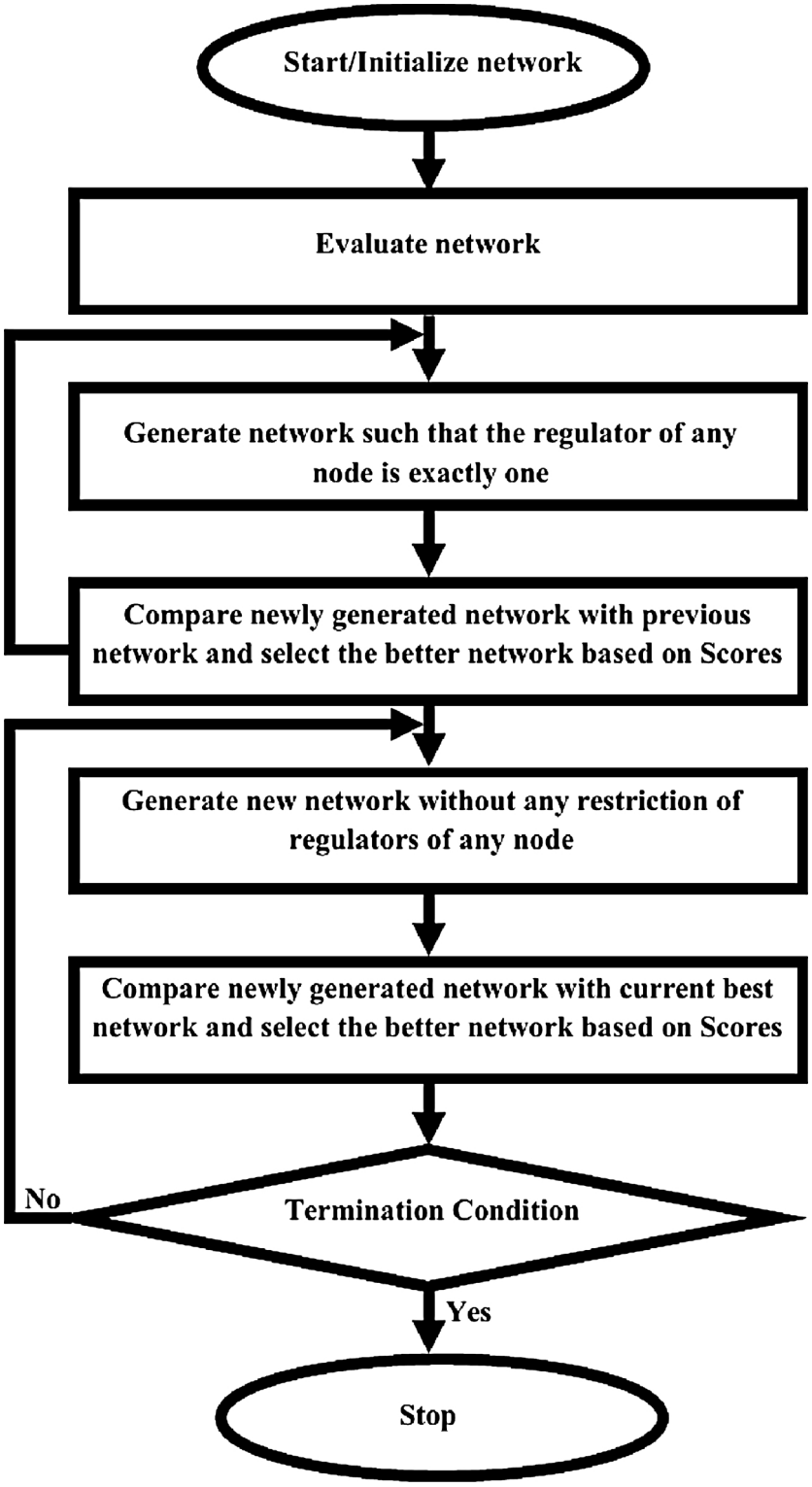

Fig. 2. Schematic description of restricted-derestricted search method for DBN. The initialization step involves the supply of a set of known (prior) relationships to guide the inference process. This is processed and compared to newly generated networks. Better scoring networks are kept for further processing in subsequent steps while low scoring networks are discarded. The procedure continues through both restricted and derestricted stages until a termination condition is met.

data) comprised of 54 genes and 51 arrays (Supplementary Table S2). The GDS4088 data represents microarray measurements from resected breast cancers. It is the results of the analysis of breast tumor samples preserved using RNA stabilization methods up to 3 h post-tumor excision. On the other hand, the GSE40066 data comprised of 43 samples from mammary gland tissues and 8 samples from cardiac blood tissues. All these samples are based on the Affymetrix MOE 430 A arrays. Furthermore, the GSE4917 data comprised of 1333 relevant Probe set identifiers and 24 arrays (Supplementary Table S3) while the TCGA data comprised 390 gene symbols and 428 samples (Supplementary Table S4). These different sizes of data permit the evaluation of methods on the combinations of nodes and samples in reconstructing

transcriptional regulatory network.

In order to obtain the relevant transcriptional regulatory relationships among transcription factors and their target cancer-related genes to serve as references (gold standard networks) for evaluating each method, we searched the Encyclopaedia of DNA Elements (ENCODE) (ENCODE Project Consortium, 2012) for transcription factors and corresponding gene targets in cancer (Supplementary Tables S5–S8). These real data sets permit us to ascertain the performance in real discovery settings of breast cancer rather than a simulated network data that may not reflect the conditions of regulatory relationships among genes in cancer. In essence, the reference network relationships are known transcription factors and corresponding targets of the human genome involved in cancer. It must be noted that subsets (of sizes 20 and 30) of existing gene-transcription factor relationships were supplied as prior networks to guide the inference (from all the data sets).

2.5. Performance indicators

We compared our method with existing high performing methods used in learning DBNs. These are based on Simulated Annealing with Re-Annealing and the Greedy Search with Random Restarts. These methods are used in the comparison because the novel search technique is an enhancement in the sequential approaches to searching for optimal solutions, particularly, greedy-based approaches. Moreover, all these methods allow the incorporation of prior knowledge to infer networks in as much as they provide high accuracies in such studies (Chickering, 1996; Yu et al., 2004).

Greedy Search with Random Restarts: The traditional greedy method applies edge changes to the current networks and the resulting network with the highest score is retained as the new network. To enhance its performance to escape from being trapped on a local optimal solution, this procedure is performed repeatedly each time with a different randomly generated initial network. This approach, called the Greedy Search with Random Restarts (GR), has performance comparable to other advanced methods and so are widely used as illustrated in (Chickering, 1996; Yu et al., 2004).

Simulated Annealing with Re-annealing: On the other hand, Simulated Annealing starts with an initial network and randomly selects an edge change from the set of possible edge changes to the network. The resulting network is accepted if it improves the score. However, if the resulting network decreases the network score, it is accepted based on a parameter of the system, temperature, T. When temperature at start is high, a lot of changes are accepted, even if the score is not improved. However, as the temperature decreases, less changes are accepted. This is continued until the desired stopping criterion is met. To enhance its performance, the temperature is allowed to increase in later parts of the method. This approach, Simulated Annealing with Re-annealing (SAR), searches high-scoring networks because of the later rise in temperature that allows the method to escape locally optimal solutions, leading to high performance (Yu et al., 2004).

In implementing any of these methods, two different edge change methods are applicable: *All-Local-Moves* and *Random-Local-Moves*. All-Local-Moves involve composing a list of all available local moves, given the current state of the network, and then select the move that yields the highest-scoring network. Random-Local-Move selects a move at random from all possible moves. Hence, by applying all these edge changes, we derived four methods which were compared with our proposed method.

The methods and a quantile discretization of all variables were implemented with the Bayesian Network Inference with Java Objects (Sladeczek et al., 2019). For simulated annealing, the temperature parameter was set to 10,000 with a 0.7 cooling factor. Terminations of methods were permitted after 10,000 restarts or 5 h. In all experiments, a minimum number of 1000 networks were explored before testing any of the stopping criteria. The optimal networks produced by these methods are examined for their performances.

In particular, we examine the sensitivities, specificities and precisions of the methods to accurately infer transcriptional regulatory relationships among the genes. Sensitivity (Eq. (5)) measures the rate of inferring true regulatory relationships among the genes, while Specificity (Eq. (6)) measures the rate of distinguishing false predictions from true regulatory relationships. For any results, we obtain the true positive (TP), false positive (FP), true negative (TN), and false negative (FN) predictions to estimate the Sensitivity and Specificity. Use is made of these parameters to also determine accuracies and Areas under Receiver Operating Characteristic (ROC) curves.

$$Sensitivity = \frac{TP}{TP + FN} \tag{5}$$

$$Specificity = \frac{TN}{TN + FP} \tag{6}$$

These metrics are consistent with such studies as exemplified in (Adabor et al., 2015; Husmeier, 2003). In addition, we also measure the precision of each the methods using Eq. (7). Precision represents the proportion of truly predicted relationships by the methods relative to all predictions. These indicate the quality of networks. It is desirable to achieve high sensitivity, specificity and precision.

$$Precision = \frac{TP}{TP + FP} \tag{7}$$

Furthermore, since the optimal networks are achieved by their scores, we also compare each of the scores (values of BDe) to investigate the correspondence between the network scores and the accuracy of inference methods. This will enable us to ascertain the best heuristic approaches that achieve high-scoring and quality networks. The results of each run of experiment are compared with the reference networks to identify which relationships were recovered in the optimal solution. Experiments are repeated in 10 different runs, and the aggregate of all results of parameters of the performance metrics are reported. A relationship in the reference network which is also predicted by a method is considered as TP. However, if a predicted relationship does not exist in the reference network, it is considered as FP. Furthermore, if a relationship exists in the reference network but not predicted by a method, then it is a FN while a TN is counted for a relationship which is absent in both the predicted and reference network relationships. In the inference from the smaller data set (GSE40066 data), the methods were tested on their abilities to recover 20 known regulatory relationships (reference network) while 149 relationships were excluded. However, for the other relatively larger data sets, the methods were tested on their abilities to recover 30 known regulatory relationships while varying the excluded relationships with respect to the gene symbols entailed in the expression data sets. The regulatory relationships are supplied as Supplementary Tables S5–S8.

3. Results

3.1. Sensitivities of dynamic Bayesian Network inference from GDS4088 and GSE40066 data sets

Transcriptional regulatory networks constructed using DBNs, as described, were shown to accurately recover relationships between transcription factors and corresponding target genes from the GDS4088 and GSE40066 data sets. More particularly, with the incorporation of prior knowledge searched from the literature, the DBN methods achieved as high as 97% rate of recovering true relationships between transcription factors and their target genes (Figs. 3 and 4). Although the Simulated Annealing methods and the methods which apply Random-Local-Moves under-performed in recovering reference network regulatory relationships based on the GDS4088 and GSE40066 data sets, the Greedy Methods with Random Restarts along with All-Local-Moves performed well (Fig. 3). On the GDS4088 data, Simulated Annealing

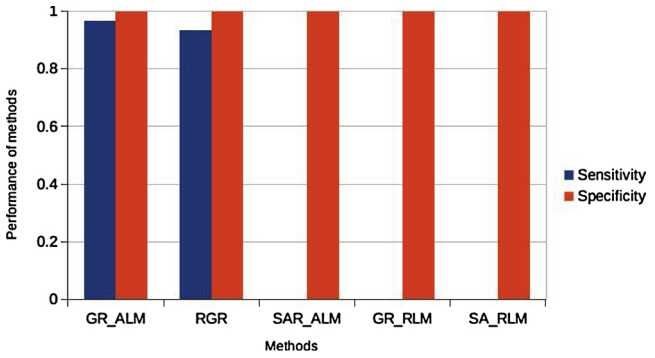

Fig. 3. Sensitivities and Specificities of dynamic Bayesian Network inference based on GDS4088 data (623 genes; 86 samples). In the experiments leading to the results, prior networks of 30 regulatory relationships were supplied to the inferring algorithms. All methods achieved perfect specificities while only the Restricted-Derestricted Greedy Method and the Greedy Method with All-Local-Moves recovered some known (reference network) regulatory relationships from the GDS4088 data. GR_ALM is Greedy Method with All-Local-Moves, RGR is proposed Restricted-Derestricted Greedy Method, SAR_ALM is Simulated Annealing with All-Local-Moves, GR_RLM is Greedy with Random-Local-Moves and SA_RLM Simulated Annealing with Random-Local-Moves.

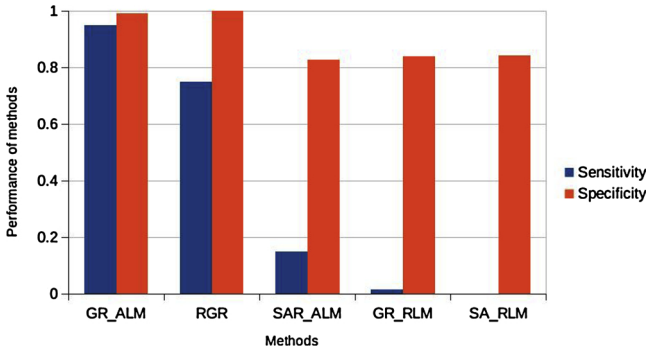

Fig. 4. Sensitivities and Specificities of dynamic Bayesian Network inference based on GSE40066 data (54 genes; 51 samples). In the experiments leading to the results, prior networks of 20 regulatory relationships were supplied to the inferring algorithms. Restricted-Derestricted Greedy Method achieved the highest specificity among all the methods while it was only second to the Greedy Method with All-Local-Moves in terms of measuring sensitivities. GR_ALM is Greedy Method with All-Local-Moves, RGR is Restricted-Derestricted Greedy Method, SAR_ALM is Simulated Annealing with All-Local-Moves, GR_RLM is Greedy with Random-Local-Moves and SA_RLM Simulated Annealing with Random-Local-Moves.

methods and the methods which apply Random-Local-Moves did not predict any of the true relationships used to evaluate the networks. This resulted in those methods achieving sensitivities of zeros.

In addition, it was noted that the sensitivity of the Greedy-based methods declined on the GSE40066 data with fewer known prior relationships among variables although they had the highest sensitivities (Fig. 4). This was a result of the fewer prior relationships supplied to guide the learning of DBN of transcriptional regulatory networks. Indeed, a smaller variable to sample ratio reduces the search space for network exploration. However, since the greedy search for networks primarily depends on the scores of the current network, high-scoring networks would be achieved irrespective of the sensitivity.

On the other hand, the Simulated Annealing methods with Random-Local-Moves improved on the smaller dimension data although they could not outperform the Greedy-based methods (Fig. 4). This was a result of the reduced number of samples in the data allowing the method to find some relationships found in the reference as it undergoes a more thorough search in the reduced set of possible networks.

Furthermore, in order to assess the performance of the methods on problems without prior networks, we repeated the same experiments with both GDS4088 and GSE40066 data sets without supplying any prior relationships to the algorithms. It was found that none of the methods was able to recover any reference network regulatory relationships among variables resulting in no reported sensitivity.

3.2. Specificities of dynamic Bayesian Network inference from GDS4088 and GSE40066 data sets

As was done to achieve the Sensitivities of the DBN methods, we investigated the ability of the methods to distinguish between predicted transcription factor/target gene relationships not found in the reference from transcriptional regulatory relationships found in the reference networks based on the GDS4088 and GSE40066 data sets. Unlike the Sensitivity, all the DBN methods performed highly in distinguishing between falsely predicted relationships from true relationships (with high specificities). More particularly, on the GSD4088 data, all the DBN methods accurately distinguished all non-existing relationships from transcriptional regulatory relationships found in the reference networks resulting in up to 100% Specificity (Fig. 3). Similarly, the Greedy-based methods along with All-Local-Moves and the novel Restricted-Derestricted Greedy Search Method were the better performers in distinguishing false relationships from true transcriptional regulatory relationships in the problem involving the GSE40066 data, i.e. compared to the Simulated Annealing-based methods and methods which apply Random-Local-Moves (Fig. 4). The differences in Specificities with regards to the two data sets are the results of the larger size of prior network used in the task involving the GDS4088 data set compared to that of the GSE40066 data. Although a previous study (Yu et al., 2004) revealed that Specificity decreased with larger data set, our findings suggest that with higher numbers of prior relationships, Specificities are higher for the task of inferring transcriptional regulatory relationships from cancer data. It must however be noted that while we explore real biological data sets, Yu et al. (2004) (Yu et al., 2004) used a simulated data. This accounts for the differences. In addition, our results are consistent with earlier studies which also found high specificities in an application of BN (Adabor et al., 2015).

Although the Sensitivities of the methods in experiments without the use of prior network relationships were poor, the methods achieved high Specificities in similar experiments without prior networks (Fig. 5). These were the results of the methods predicting fewer relationships which were not found in the reference network (false positive) compared to TN predictions.

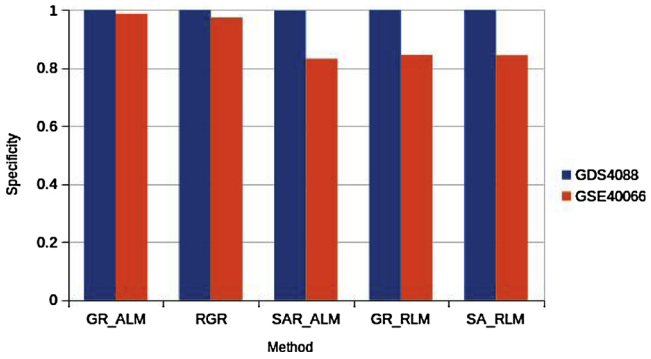

Fig. 5. Specificities of dynamic Bayesian Network inference based on GDS4088 and GSE40066 data sets. Experiments were performed without supplying prior network of regulatory relationships to the inferring algorithms. The Restricted-Derestricted Greedy Method performs equally with the Greedy method with All-Local-Moves while it achieved better specificities than the other DBN inference methods when applied to the GSE40066 data. GR_ALM is Greedy method with All-Local-Moves, RGR is Restricted-Derestricted Greedy Method, SAR_ALM is Simulated Annealing with All-Local-Moves, GR_RLM is Greedy with Random-Local-Moves and SA_RLM Simulated Annealing with Random-Local-Moves.

Table 1
Accuracy and Precision of dynamic Bayesian Network inference from GDS4088 and GSE40066 data sets.

	GDS4088		GSE40066	
Method	Accuracy	Precision	Accuracy	Precision
Greedy ALM[a]	1	1	0.99	0.95
Restricted-derestricted greedy	1	1	0.97	1
Simulated Annealing ALM[a]	0.99	0	0.76	0.09
Greedy RLM[b]	1	0	0.76	0.01
Simulated Annealing RLM[b]	1	0	0.76	0

[a] Simulated Annealing with All-Local-Moves.
[b] Method with Random-Local-Moves.

3.3. Accuracy and precision of dynamic Bayesian Network inference from GDS4088 and GSE40066 data sets

The effectiveness of the DBN methods for reverse-engineering transcriptional regulatory relationships among genes from the data sets was also demonstrated in the measurements of accuracies and precisions. Particularly, the Restricted-derestricted greedy method achieved the best precision on the GSE40066 data set (100%) while it performed equally with the traditional Greedy method with All-Local-Moves on the GDS4088 data (Table 1). The importance of the Restricted-derestricted greedy method was demonstrated when it achieved accuracies consistent with those of Greedy method with All-Local-Moves when applied to the GDS4088 and GSE40066 data sets (Table 1). These were expected since both methods predicted similar numbers of TN and TP. The fact that the Simulated Annealing-based methods had lower or no precisions (Table 1) indicates that they are less effective compared to the greedy-based methods when applied to recover dynamic BNs based on the data. Nevertheless, the Simulated Annealing-based methods improved accuracies because they were able to predict high numbers of TN. These suggest that although the Simulated Annealing-based methods may be outperformed by the Greedy-based method, they can truly predict non-existing transcriptional regulatory relationships among genes in cancer.

3.4. Performance of dynamic Bayesian Network inference methods on GSE4917 and TCGA data sets

To further assess the performance of the DBN methods for reverse-engineering transcriptional regulatory relationships among genes in cancer, additional experiments with prior networks were performed with the GSE4917 (1333 genes; 24 samples) and the TCGA (390 genes; 428 samples) data sets. The methods were compared on the basis of accuracies and the areas under ROC curves. For the experiments using the GSE4917 data, a perfect discrimination between sensitivity (True Positive Rate) and False Positive rate (1 minus specificity) was observed for both the novel Restricted-derestricted method and the Greedy Method with All-Local-Moves (Fig. 6). Besides the Simulated annealing with random-local-moves method which had lower accuracy because its curve fell below a random model, the other DBN methods performed better on the GSE4917 data with high areas under the ROC curves (Fig. 6 and Table 2). The performance of the methods on the GSE4917 data involving 1333 nodes indicates the potential of our method and the others to be successfully applied to high variable datasets to decipher transcriptional regulatory relationships among genes in cancer. However, for such data sets with high number of variables (nodes), simulated annealing with random-local-moves approach is not recommended because it achieved lower area under ROC curve (Table 2). On the other hand, all the methods with random-local-moves performed equally as a random model on the TCGA data involving 390 nodes (Fig. 7). However, all the methods using all-local-moves and the Restricted-derestricted method achieved better trade-off between

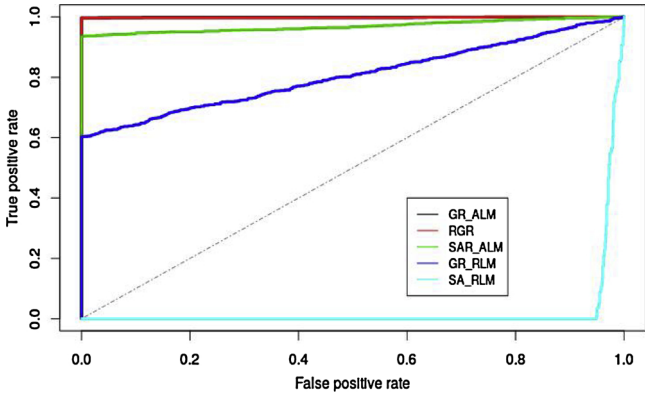

Fig. 6. Performance of dynamic Bayesian Network inference methods on GSE4917 data. In the experiments leading to the results, prior networks of 30 regulatory relationships were supplied to the inferring algorithms. The proposed Restricted-Derestricted Greedy Method provides perfect accuracies in recovering transcriptional regulatory relationships in cancer as does the Greedy method with All-Local-Moves. However, SA_RLM Simulated Annealing with Random-Local-Moves has very poor performance even though Simulated Annealing with All-Local-Moves outperforms Greedy with Random-Local-Moves. GR_ALM is Greedy method with All-Local-Moves, RGR is Restricted-Derestricted Greedy Method, SAR_ALM is Simulated Annealing with All-Local-Moves, GR_RLM is Greedy with Random-Local-Moves and SA_RLM Simulated Annealing with Random-Local-Moves.

Table 2
Areas under ROC curves and Measures of accuracies of dynamic Bayesian Network inference from GSE4917 and TCGA data sets.

	GSE4917		TCGA	
Method	AUC*	Accuracy	AUC*	Accuracy
Greedy ALM[a]	1	1	1	1
Restricted-derestricted greedy	1	1	1	1
Simulated Annealing ALM[a]	0.97	0.97	0.99	0.97
Greedy RLM[b]	0.81	0.90	0.50	0.99
Simulated Annealing RLM[b]	0.02	0.90	0.50	0.99

* AUC is Area under ROC curve.
[a] Method with All-Local-Moves.
[b] Method with Random-Local-Moves.

sensitivity and specificity to indicate that they were very accurate (Fig. 7). Particularly, the Restricted-derestricted method achieved a perfect area under ROC curve to suggest that it performs favourably well compared to some existing methods. A summary of the areas under ROC curves and the accuracy of the methods applied to the GSE4917 and TCGA data sets are presented in Table 2.

Furthermore, in order to assess the best methods in terms computational cost, we compare Greedy method with All-Local-Moves and Restricted-derestricted methods since they are the better performers in all the experiments conducted in the study. Here, the number of restarts for each of the methods is determined for fixed amounts of time on personal computer with 8GB RAM and 1TB HD. This allows the determination of cost for completing inference by the methods under the same conditions at any particular time. Thus, the higher the number of restarts by a method, the less the time it will take to complete similar tasks. The cost-effective method should, therefore, have the highest number of restarts for a fixed time. In this test, it was found that the Restricted-derestricted method was computationally less costly, having achieved a significantly higher number of restarts compared to the Greedy method with All-Local-Moves ($p = 5.41e\text{-}6$). This was observed after the methods were made to recover transcriptional regulatory networks from TCGA data over the fixed times 1, 2, 3, 4 and 5 h in experiments involving prior networks and those without prior networks (**Supplementary Material**). The Restricted-deristricted method is

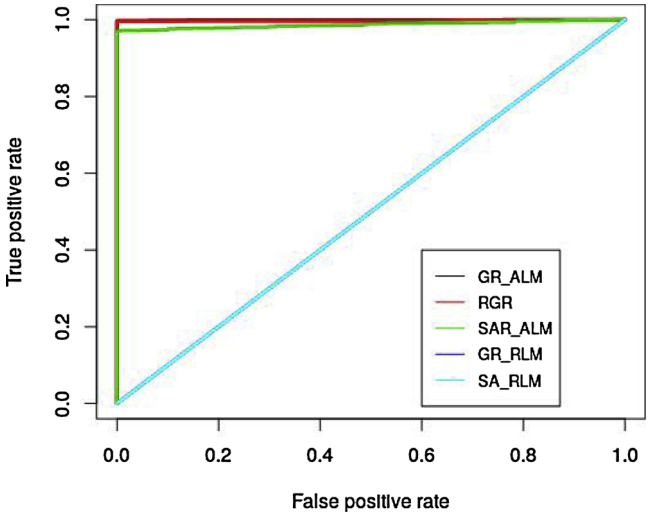

Fig. 7. Performance of dynamic Bayesian Network inference methods on TCGA data. In the experiments leading to the results, prior networks of 30 regulatory relationships were supplied to the inferring algorithms. Methods involving Random-Local-Moves could only perform as would a random model. The Restricted-Derestricted Greedy Method achieved excellent accuracies in predicting regulatory relationships from the TCGA data. GR_ALM is Greedy method with All-Local-Moves, RGR is Restricted-Derestricted Greedy Method, SAR_ALM is Simulated Annealing with All-Local-Moves, GR_RLM is Greedy with Random-Local-Moves and SA_RLM Simulated Annealing with Random-Local-Moves.

computationally less costly because of its restricted preliminary inference stage.

3.5. Relationship between networks scores and other performance indicators

Furthermore, due to the differences in the measures of Specificity and Sensitivity, we investigated the relationships between network scores and the metrics of the quality of network. This is particularly noteworthy since the quality of each method is obtained from the evaluation of the optimal network achieved. All the methods preferably select networks with the best scores from all explored networks during inference. The scores of the networks were found to be more strongly correlated with the Specificity of the methods ($r = -0.89, p = 1.68e\text{-}07$) compared to Sensitivity ($r = -0.15, p = 0.52$). The correlation coefficients were determined by the Spearman's rank method because it is robust and suited for the comparison between the scores and the performance metrics which are all based on optimal networks. The correlation coefficients suggest that the scores have inverse relationships with both the sensitivity and specificity.

In order to examine the specific contribution of the scores of networks to Specificity of the methods, we derived a linear regression model (Table 3) which revealed that 48% of the variations in Specificity are explained by the scores of the network. This is very significant because transcriptional machinery is very complex and has multiple transcription activators and repressors, who themselves are affected by mass upstream signalling and other events unaccounted for by the DBN

Table 3
Scores of networks predict Specificity of dynamic Bayesian Network inference methods.

Variable	Regression coefficient	p-value
Scoring Metric	−1.26e-06	6.57e-04[b]
[a]Constant	8.95e-01	< 2e-16[b]

[a] Constant represents variables affecting regulatory relationships among variables which are not accounted for by the model.
[b] Variable is statistically significant at a 5% significance level.

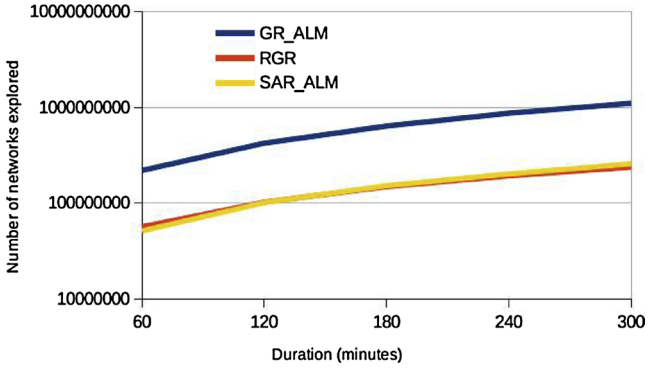

Fig. 8. Exploration of networks by three methods dynamic Bayesian network. Number of networks is the mean number of explored over 300 min by methods. The Restricted-Derestricted method explores sufficiently significant networks with higher sensitivities and specificities. GR_ALM is greedy method with All-Local-Moves, RGR is Restricted-Derestricted Greedy Method and SAR_ALM is Simulated Annealing with All-Local-Moves.

methods. Moreover, the model indicates that, on average, there is a statistically significant marginal decrease in Specificity of the methods in learning transcriptional regulatory networks for every unit increase in the BDe scores of networks (Table 3). These results posit that methods that balance scores and quality of optimal networks are advantageous.

3.6. Restricted-derestricted dynamic Bayesian network has improved network scores and other performance indicators

Knowing that all the methods perform differently with regards to Sensitivity while they maintain higher Specificities, we further explore the search for optimal networks of each method using the GDS4088 and GSE40066 data sets. In particular, after performing 10 experiments for 3 best-performing methods which apply All-Local-Moves namely Greedy, Simulated Annealing and Restricted-Derestricted methods, we found that the Greedy method explores larger number of networks over time compared to both the Simulated Annealing and the Restricted-Derestricted method (Fig. 8). Nevertheless, the number of networks explored by all the methods increases in the same manner as the time of the inference increases (Fig. 8). This was because the methods progress with the search for better networks until the search is terminated. However, the Greedy search easily makes transitions to explore newer networks leading to higher numbers of networks since it only requires any edge change that improves the network scores to progress. On the other hand, the other two methods limit the search by introducing additional constraints required before progressing to explore subsequent networks. More specifically, the Simulated Annealing sometimes accepts a new network with lower score depending on a functional value of temperature. Also, the Restricted-Derestricted method also permits initial exploration of networks to only those having fewer parents than required before later allowing the required number of parents to be explored. Although these methods are associated with lower numbers of explored networks compared to the Greedy method, they always find networks with the best scores as a result of the enhancement in the search of high-scoring networks (Table 4).

DBN inference methods based on Simulated Annealing had the best network scores in all experiments (Table 4). This was a result of the intrinsic capacity of the Simulated Annealing methods to escape lower local optimal scoring networks to find better scoring networks although this compromises the quality of network. However, the advantage of the Restricted-Derestricted search over the Greedy search is revealed in these experiments as they provide well improved network scores. Even though the Restricted-Derestricted finds better scoring networks, it does not compromise on the quality of networks since it achieves perfect

Table 4
Mean scores of optimal networks achieved with GDS4088 and GSE40066 data sets.

Method	Inference from GDS4088 data		Inference from GSE40066 data	
	Presence of prior network	Absence of prior network	Presence of Prior network	Absence of prior network
Greedy ALM[a]	−84539.48	−83334.34	−3606.93	−3371.51
Restricted-derestricted greedy	−84480.07	−83324.73	−3565.19	−3359.19
Simulated Annealing ALM[a]	−83280.26	−83280.26	−3296.16	−3303.31
Greedy RLM[b]	−83325.57	−83326.58	−3310.27	−3311.09

[a] Method with All-Local-Moves.
[b] Method with Random-Local-Moves.

accuracies in recovering transcriptional regulatory networks as the Greedy method with all-local-moves (Table 4). This high performance in achieving better network scores while maintaining quality optimal networks is a result of the preliminary restrictions to allow the transcription factors to target genes of primary importance before exploring other possible relationships that may exist in subsequent phases of the method. Thus, the Restricted-Derestricted DBN provides the desirable balance between finding high scoring and quality networks.

4. Discussion

The advent of high-throughput technologies has made it possible to generate huge data sets from which underlying biological insights can be extracted. These rely heavily on efficient computational approaches to effectively unearth biological insights. In the case of reverse-engineering networks of transcriptional regulatory relationships among genes, there have been a plethora of algorithms for inferring networks of transcription factor-target gene interactions. These have included clustering algorithms (Eisen et al., 1998), Information Theoretic-based approaches (Stuer et al., 2002; Butte AJ Kohane, 2000; Faith et al., 2007; Margolin et al., 2006; Meyer et al., 2007), and ODE-based methods (Gardner et al., 2003; Di Bernardo et al., 2005). However, probabilistic approaches such as BN applied to such a task have the advantages that they are suitable for modelling the complex stochastic process of gene regulation, incorporate knowledge of interactions among genes in priors, and are able to cope with noise present in expression data. For an extended application to model feedback loops, it is desirable to develop more efficient methods to find optimal DBNs which can identify transcriptional regulatory relationships among genes with higher accuracies. To this end, we present Restricted-Derestricted DBN for inferring transcriptional regulatory networks. We apply our method to actual biological data in the context of inferring networks in cancer in order to establish its relevance and applicability to uncover true transcriptional relationships among genes. This is particularly important since veritable data of transcription factor-target gene interactions are increasingly becoming available through advancements in technologies (ENCODE Project Consortium, 2012; Joshi-Tope et al., 2005). Unlike a recent study which could achieve highest accuracies of 0.55 and 0.8 in reconstructing non-Homogeneous DBNs from two synthetically curated datasets (Kamalabad and Grzegorczyk, 2018), we achieved better accuracies using real data sets for reasons stated earlier.

Most importantly, the relevance of DBN approaches applied to such tasks was proven when they were able to recover transcriptional regulatory relationships with high Sensitivity, Specificity, precision, accuracies and areas under ROC curves (up to 100%) from data sets used in this study. These performances were achieved as a result of informative prior relationships derived from the literature and used as input for the methods. This resulted in the high accuracies for Greedy-based methods with All-Local-Moves although the SAR methods and methods which apply Random-Local-Moves edge changes performed poorly. The relevance of such known prior relationships in improving reverse-engineering methods are consistent with previous studies who also found similar results after supplying priors to the inferring algorithms (Husmeier, 2003; Hartemink et al., 2002).

Additionally, our proposed Restricted-Derestricted DBN achieved performances comparable with the Greedy search method on all data sets even though it is well supported by interactions between transcription factors and target genes. The higher performances of the Greedy methods were because repeated random restarts enable the methods to escape from being trapped on a search among less network space of true relationships. Particularly, high Sensitivities of the Greedy-based methods are not different from those achieved in earlier studies which also found such high performances (Adabor et al., 2015; Yu et al., 2004). On the other hand, although the Simulated Annealing methods escape being trapped on local optimal networks, they do not guarantee high quality networks. Thus, SAR performs a more rigorous search for better networks with less or no considerations of quality of relationships as is required for a good application to learning transcriptional regulatory networks from real breast cancer data.

Further, although Random-Local-Moves applied to the methods facilitate quicker searches for networks because only one edge change in the network is required to progress, it also fails to capture important relationships between variables of the network. Hence, although it results in better BDe scores, it produces networks of relationships which are less relevant. Remarkably, as have been shown, the sensitivity is inversely related to the scores of optimal networks achieved by the methods. This suggests that achieving higher scoring networks does not necessarily imply that the methods are appropriate for inferring transcriptional regulatory relationships among genes compared to other methods with better performance. However, our approach is able to establish better scoring networks as well as infer accurate relationships among variables. This is the added advantage of the Restricted-Derestricted DBN over the existing methods. These highlight the potential of Restricted-Derestricted DBN to infer accurate transcriptional regulatory networks involving feedback loops.

Moreover, the Restricted-Derestricted DBN has the potential to identify inaccurate transcriptional regulatory relationships as well as the other DBNs as it achieved perfect accuracies and areas under ROC curves (Table 2). Although these performances are comparable with the Greedy method random-local-moves, the Restricted-Derestricted search method produces better network scores to support its usefulness over the others (Table 4). Indeed, all the DBNs used here are able to distinguish inaccurate relationships from accurate regulatory relationships. Even the worst performing methods achieved Specificities of at least 83.24%. Besides, an inverse linear relationship was found to exist between scores and the Specificities of the methods. This is attributable to higher specificities for low scoring-networks achieved by the greedy-based methods compared to other methods which achieve high scoring networks. In addition, our analysis of the relationships between the quality and score metric which evaluate DBNs suggests that optimal networks achieved on the basis of scores by the methods correspond more to Specificity of methods compared to Sensitivity when applied to the inference problem in this study.

In this work, we found that Greedy-based methods involving All-Local-Moves along with the proposed Restricted-Derestricted DBN have

high performances in recovering transcriptional regulatory relationships in cancer. However, to obtain a balance between high-scoring networks with better accuracies (true recoveries); the Restricted-Derestricted method performs better. This method for inferring DBN is different from the approach for static BNs in which, progressively, candidate solutions are restricted by a set of forbidden parents during the learning process (Gamez et al., 2011).

5. Conclusion

Transcriptional regulatory networks provide insights into regulator gene and target gene interactions that are crucial to understanding the etiology of diseases. With the existence of self- and feedback- relationships, dynamic Bayesian networks provide accurate predictions of the relationships that exist in transcriptional regulatory networks. We have proposed Restricted-Derestricted approach for learning DBNs. This method compares favourably with other methods to recover transcriptional regulatory networks with high accuracies in as much as it is motivated by transcription factor-gene interactions in cancer. Our method employs an interpretable search strategy that corresponds with the dynamic transcription factor-target gene relationships.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.compbiolchem.2019.02.006.

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