Computational reconstruction of transcriptional relationships from ChIP-Chip data

Ngoc Tu Le, Tu Bao Ho, and Bich Hai Ho

Abstract—Eukaryotic gene transcription is a complex process, which requires the orchestrated recruitment of a large number of proteins, such as sequence-specific DNA binding factors, chromatin remodelers and modifiers, and general transcription machinery, to regulatory regions. Previous works have shown that these regulatory proteins favor specific organizational theme along promoters. Details about how they cooperatively regulate transcriptional process, however, remain unclear.

We developed an unbiased method to reconstruct a Bayesian network-based model representing functional relationships among various transcriptional components. Independently, the positive(+)/negative(-) influence between these components was measured from protein binding and nucleosome occupancy data and embedded into the model. Application on *S.cerevisiae* ChIP-Chip data showed that the proposed method can recover confirmed relationships, such as Isw1-Pol II, TFIIH-Pol II, TFIIB-TBP, Pol II-H3K36Me3, H3K4Me3-H3K14Ac, etc. Moreover, it can distinguish co-locating components from functionally related ones. Novel relationships, e.g., ones between Mediator and chromatin remodeling complexes (CRCs), and the combinatorial regulation of Pol II recruitment and activity by CRCs and general transcription factors (GTFs), were also suggested.

Conclusion: Protein binding events during transcription positively influence each other. Among contributing components, GTFs and CRCs play pivotal roles in transcriptional regulation. These findings provide insights into the regulatory mechanism. Also, the proposed method can be extended to reconstruct more accurate model as new data become available.

Index Terms—Transcriptional relationship, Bayesian network, ChIP-Chip data, histone modification, nucleosome positioning, chromatin remodeling complex

1 Introduction

Transcription in the context of chromatin is a complex process with the purpose of activating a set of genes in response to environmental stimuli. Nucleosome, the fundamental unit of chromatin formed by wrapping 147bp of DNA around an octamer of histone proteins [1], is known to function as the barrier preventing the access of transcriptional components to DNA sequences. To facilitate transcription in such context, in addition to general transcription machinery, e.g., activators, Mediator, GTFs, and Pol II, the cell must resort to other factors, such as chromatin remodelers and modifiers. The main function of these factors is to alter the interactions of histone-DNA or histone-histone, by which transcription machinery can gain access to *cis*-regulatory elements to initiate the process [2], [3]. Elucidating the interplay of various components involved in transcription is therefore a critical step toward understanding gene regulation.

Technological advances for studying protein-DNA interactions on large scale, e.g., the combinations of chromatin immunoprecipication (ChIP) with high-throughput technologies including DNA microarray (ChIP-Chip) or massively parallel sequencing (ChIP-Seq), have made it possible to produce genome-wide maps of various transcription-related components, such as general transcription machinery and its regulators [4], nucleosomes [5], [6], transcription factors (TFs) [7], [8], histone modifications [9], [10], and other chromatin components [11]. The availability of such data offers unprecedented opportunities to computationally uncover their genome-wide relationships. For example, Wang *et al.* reconstructed a whole-genome map of transcriptional cooperativity among TFs from mapping data [12]; Dai *et al.* identified statistically significant interactions between CRCs and post-translational modifications of histone proteins in *S.cerevisiae* [13]; Stenseel *et al.* reconstructed targeting interactions among 43 chromatin components in *Drosophila* cells [14]. To our knowledge, however, most of the previous works on transcriptional network reconstruction only concentrated on investigating the interactions of either TFs-TFs, TFs-genes, or genes-genes [15]. Consequently, the role of each component as well as how they cooperatively regulate transcriptional process remain elusive. In other words, the whole picture of functional relationships among transcriptional components is far from complete.

We propose a novel computational method, as an extension of our previous work on reconstructing histone modification network from ChIP-Chip data

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[16], to address the above-mentioned problem by reconstructing a Bayesian network-based model representing functional relationships among various transcriptional components. Firstly proposed by Friedman *et al.* to discover gene interactions from expression data [17], Bayesian network (BN) models have been widely applied to reconstruct many kinds of biological networks, such as protein-protein interactions [18], [14], protein signaling networks [19], and interactions among histone modifications [20]. Employing the search-and-score approach, we develop an unbiased method to infer network structure in the context where no positive training data is available. Moreover, based on the observation that transcriptional components all work on chromatin substrate and cause change in nucleosome organization, the positive(+)/negative(-) influence between any two functionally related components was measured from binding and nucleosome positioning data and integrated into the network model.

When applied on genome-wide ChIP-Chip data of 36 transcriptional components in *S.cerevisiae*, including general transcription machinery, chromatin remodeling complexes, and histone modifications, our method not only recovers previously confirmed relationships, e.g., Rsc9-Rfx1, Isw1-Pol II, TFIIH-Pol II, Pol II-H3K36Me3, TFIIH-H3K4Me3, H3K4Me3-H3K14Ac, but also suggests several new ones, e.g., Mediator-CRCs, (CRCs,GTFs)-Pol II, which may provide insights into transcriptional regulation. Resulting network model showed that transcriptional components positively influence each other. Among them, GTFs, Mediator, and CRCs play critical roles in regulating the outcome of the whole process. Our method can also be extended to reconstruct more accurate model as data on other aspects of transcription become available.

2 METHODS

2.1 Materials

2.1.1 Histone modification

Genome-wide ChIP-Chip data of 8 histone modifications, including H3 K9Ac/K14Ac, H4Ac, H3K4Me1/2/3, H3K36Me3, and H3K79Me3, were taken from Pokholok *et al.* [21]. Modification levels at each promoter, defined as the region from 500bp upstream to 100bp downstream around Transcription Start Site (TSS), were measured as the averages of overlapping probes or the nearest one, in case of no overlap.

2.1.2 Protein binding

Binding data of diverse representative components of the gene regulatory machinery in *S.cerevisiae*, including 8 sequence-specific transcription factors (TFs), 8 chromatin remodelers, 6 GTFs and TATA-binding protein (TBP), 2 components of Pol II, and 3 components of Mediator, were taken from Venters and Pugh [4]. Binding profile at the promoter of these components was assigned as the average of binding levels of corresponding TSS and Upstream Activating Sequence (UAS). After removing promoters lacking binding information and combining with histone modification data above, we received a contingency table of 36 columns and 4498 rows for further analysis.

2.1.3 Nucleosome occupancy

Genome-wide nucleosome occupancy data at 4bp resolution were taken from Lee *et al.* [22]. Occupancy profile for each promoter was derived as follows. At first, the promoter was divided into 4 bins of 150bp long. Then, bin occupancy value was calculated as the sum of the occupancy levels of all probes belonging to the bin. Each occupancy profile was finally represented by a 4-dimensional vector.

2.1.4 Genomic annotations

Genomic annotations of *S.cerevisiae* (SGD/sacCer2 assembly) were extracted from the tables provided by the UCSC Genome Browser [23].

2.2 Bayesian network

2.2.1 Definition

A Bayesian network (BN) for a set of variables $\mathbf{X} = \{X_1, X_2, \ldots, X_n\}$ is a probabilistic model consisting of two components [24], [25]:

- A network structure S, which is a directed acyclic graph (DAG), representing conditional (in)dependence relationships among variables in $\mathbf{X}$.
- A set P of local probability distributions associated with each variable.

Markov condition guarantees that these two components, (S, P), encode a joint probability distribution on $\mathbf{X}$, given by:

$$p(\mathbf{x}) = \prod_{i=1}^{n} p\left(x_i | \mathbf{Pa}_i\right)$$

in which the terms of the product on the right hand side correspond to the local probability distributions P and $\mathbf{Pa}_i$ are the parents of x_i. The number of parents of each variable is usually small, so a BN provides a compact and convenient way to represent a joint probability distribution. In our work, we learned a BN on discrete variables, thus local probability distributions P can be represented by Conditional Probability Tables (CPTs). One such table specifies the probability a variable takes a certain value given the values of its parents.

2.2.2 Learning BN structure.

As mentioned above, a BN contains two components. Thus, there are two steps in learning a BN model from data: parameter learning, which specifies the local probability distributions P, and structure learning, which identifies the structure S. The main target of our work is to uncover the dependencies among transcriptional components, hence we focus on the latter learning problem.

Score-based search method was employed to learn a BN structure representing the dependencies among transcriptional components. The aim of this method is to identify network structures that "best" describe the data by some measure. A search procedure, starting from an initial structure (a graph without any edges), explores the space of possible network structures step-by-step. At each step, it scores the corresponding structure to identify the network with maximum score. Because exhaustive search in the structure space is infeasible [26], a greedy hill-climbing search was used as our search strategy. To escape from local maximum, a simulated annealing approach was used.

To score a candidate network, we used a Bayesian scoring metric, which was originated from [27], and further developed by [24] as Bayesian metric with Dirichlet prior and equivalence (BDe) metric:

$$p(S|D) \propto p(S)\prod_{i=1}^{n}\prod_{j=1}^{q_i}\left[\frac{\Gamma(N_{ij}^{'})}{\Gamma(N_{ij}^{'}+N_{ij})}\prod_{k=1}^{r_i}\frac{\Gamma(N_{ijk}^{'}+N_{ijk})}{\Gamma(N_{ijk}^{'})}\right]$$

where n is the number of variables, N_{ijk} is the number of instances in the data set D having variable x_i in state k with its parents in the j-th instantiation in current structure S, $N_{ij} = \sum_{k=1}^{r_i} N_{ijk}$ and $\Gamma(.)$ is Gamma function. $N_{ijk}^{'}$ and $N_{ij}^{'}$ have the same meaning but correspond to prior knowledge for the parameters. When no prior knowledge is available, they can be estimated as $N_{ijk}^{'} = N/(r_i q_i)$ with N is the equivalence sample size, r_i is the number of states of variable x_i and q_i is the number of instantiations of the parents of variable x_i. Finally, $p(S)$ is the prior probability of the structure. In our work, we assumed the uniform distribution on the structure S.

2.2.3 Bootstrapping and selection of the cut-off threshold

As the search-and-score method may output a different network on each run, the highest scored graph, the bootstrapping method, proposed by Friedman *et al.*[17], was employed to estimate the confidence score for each edge in the resulting network. Given a dataset D of N instances, a new dataset $D^{'}$ was created by resampling from D with replacement N times. Then a BN was inferred on $D^{'}$. These two steps of resampling and inferring a BN were repeated m times, generating m different BNs. The confidence score of each edge was estimated as the proportion of networks containing that edge. A threshold, named τ, was chosen to decide whether an edge was included in the resulting network or not.

Because there is no positive training data about the relationships among transcriptional components, we derived the following method to select the reasonable value for τ. At first, the input data D was split into two equal parts, D_1 and D_2, T times. Each time, three bootstrapped BNs corresponding to D, D_1 and D_2, named $globalBN$, $partialBN_1$, and $partialBN_2$, respectively, were learned as above. Then, we defined a measure, acc_i:

$$acc_i = \frac{\sharp(partialBN_i \cap globalBN)}{\sharp(partialBN_i)}, i = \{1, 2\}$$

where the denominator is the number of edges of $partialBN_i$ and the numerator is the number of edges that appear in both $partialBN_i$ and $globalBN$.
The selection criteria was chosen as:

$$Stability = \sum_{i=1}^{2} SNR(acc_i)$$

where $SNR(acc_i)$ is the signal-to-noise ratio of acc_i after T times of data splitting and network learning steps. It is easy to see that acc_i $(i = \{1, 2\})$, thus $Stability$, are the functions of τ. We then chose τ that maximized $Stability$ as the cut-off threshold.

2.3 Partial correlation

Assume that X and Y are two random variables and $\mathbf{Z} = (Z_1, Z_2, ..., Z_p)$ is a set of controlled random variables. Partial correlation is employed to measure the relationship between X and Y after eliminating the influence of $\mathbf{Z}$. The relationship between X and $\mathbf{Z}$ can be estimated via a linear regression model $X = \alpha_X + \mathbf{Z}\beta_X + \mu_X$, similarly for that between Y and $\mathbf{Z}$. The partial correlation between X and Y while controlling $\mathbf{Z}$ is measured as the Pearson correlation between μ_X and μ_Y.

3 Results and Discussion

3.1 Reconstruction of the network model

3.1.1 Discretization.

The contingency table described in *Materials* was used as input for the network inference algorithm. Our network model only accepts discrete variables, so the next step is to transform data into discrete values. In our work, each feature was discretized into 3 categories: "low" (0), "medium" (1), and "high" (2), using 3 different discretization schemes. The ranges were either 0th-10th, 11th-90th, 91th-100th percentile (Scheme 1), or 0th-20th, 21th-80th, 81th-100th percentile (Scheme 2), or 0th-33th, 34th-67th, 68th-100th percentile (Scheme 3), for each feature. For each

scheme, following steps were employed to infer network models.

3.1.2 Setting for BN Inference.

The structures of static BNs were inferred with Banjo (http://www.cs.duke.edu/∼amink/software/banjo/), which supports the network model described in *Methods*. Empirical running showed that, with more than $1,300,000$ search iterations the network score was not significantly improved, so each search was set to finish at this number of iterations.

3.1.3 Threshold Derivation.

The procedure described in section *Methods* was employed to derive a reasonable threshold on confidence scores of each inferred relationship, i.e., an edge of the resulting BN. We randomly split input data into two equal datasets 10 times ($T = 10$), resulting in 20 datasets. For each, we ran bootstrap procedure 100 times ($N = 100$) and derived a corresponding consensus BN. Each edge of the consensus BN had a confidence score, measured by the number of times it appeared in 100 bootstrapped BNs. Threshold τ was searched in the range of $[0.5; 0.9]$ with step of 0.05. Table 1 shows the values of the selection criterion $Stability$ with corresponding values of τ for each discretization scheme. The value of τ and the discretization scheme that gave the highest value to $Stability$, $\tau = 0.6$, $Scheme\ 2$, and $Stability = 72.2043$, were chosen. To infer the network structure, bootstrap procedure was run 1000 times on the whole data to identify confidence score for each edge. Finally, after setting $\tau = 0.6$, we received a BN of 48 edges (Fig. 1), representing functional relationships among transcriptional components in question. Confidence scores of the network are given in the supplementary material, which can be found on the Computer Society Digital Library at http://doi.ieeecomputersociety.org/Date/ID.

3.2 Transcriptional components show positive effects on each other

One disadvantage of BN in modeling biological interactions is that it does not contain information about positive(+)/negative(-) influence between the variables. For example, it is hard to know whether the binding of one protein would promote or inhibit the binding of another protein from the corresponding network model [14]. To enhance the semantic of BN models, one can impose constraint on the sign (+ or -) of each edge and learns it directly from model parameters [28], [29]. This approach, however, increases the cost of model reconstruction. Furthermore, because the signs are deduced from the highest scored graph, it is not appropriate in our context, where the resulting model is inferred from the consensus graph. Hence, we propose an alternative way to derive the signs of the relationships among transcriptional components. From the observation that these components all work on chromatin substrate and they either directly or indirectly alter nucleosome organization [30], the influence between two components was measured as the sign (+ or -) of their partial correlation value considering nucleosome profile as controlling variables. Concretely, nucleosome profile of the promoter was represented by a 4-dimensional vector, $(Occ_1, Occ_2, Occ_3, Occ_4)$, where Occ_i $(i = 1, \ldots, 4)$ was the nucleosome occupancy level at bin i (see *Methods*). Partial correlation was computed for the two components based on their binding profiles with nucleosome profile as 4 controlling variables.

The result, available in the supplementary material on the Computer Society Digital Library at http://doi.ieeecomputersociety.org/Date/ID, shows that almost all relationships were marked as positive (+), i.e., regulatory components may positively influence the activity of each other. This is consistent with the observation that during transcription, especially at initiation stage, regulatory components are cooperatively recruited and the bindings of some components may promote the bindings of the others to facilitate the process. Notably, we found two relationships marked as negative, $H3K4Me3 \rightarrow H3K4Me1$ and $PolII(Rpo21) \rightarrow TFIIA(Toa2)$. The former is supported by the finding of Morillon *et al.* that the appearance of H3K4Me3 was coincident with the drop of H3K4Me1 at the promoter of MET16 gene [31]. Though, we did not find any direct evidence for the latter one. It is possibly due to the removal of GTFs, including TFIIA (Toa2), after the full PIC is assembled and move to elongation step. Another relationship also reported by Morillon *et al.* is the negative effect of Isw1 on the activity of Pol II. In [31], Isw1 is assumed to be recruited to the promoter of MET16 to prevent the moving of Pol II and the early onset of transcription. The link $Isw1 \rightarrow PolII(Rpo21)$ in our model, however, was assigned with positive mark. This contradiction may be explained by the combinatorial effects of other co-locating CRCs, such as Ino80, Rsc9, and Swi3, on the activity of Isw1 [32].

3.3 Resulting network model confirms previously reported relationships

Comparing the occupancy of transcription machinery and chromatin regulators at promoter regions, Venters *et al.* [4] found that they were clustered into 6 groups whose members occupied a common set of genes, including {Isw2,Ioc2,Ioc3,Rsc9}, {Tfg1,Tfa1,Swr1,Taf1}, {Swi3,Ino80,Isw1,Spt3}, {Ssl1,Sua7,TBP}, {Nut1,Srb5,Rgr1}, and {Rpo21,Toa2}. Their further investigation of the "location-linkage" between sequence-specific TFs and CRCs showed that Rap1, Ifh1, and Cin5 did not exhibit significant co-occupancy with any tested CRCs, while Rfx1, Xbp1, and Yap6 showed strong co-occupancy with all tested CRCs except SWI/SNF

TABLE 1
The value of *Stability* with corresponding τ and discretization scheme

τ	*Stability (Scheme 1)*	*Stability (**Scheme 2**)*	*Stability (Scheme 3)*
0.5	36.8696	54.858	62.9467
0.55	46.7434	49.9313	48.9445
0.6	54.2189	**72.2043**	49.7512
0.65	43.4048	66.1212	36.767
0.7	38.7191	70.4882	37.2507
0.75	40.7891	27.0812	37.0849
0.8	32.5331	29.6679	45.0156
0.85	26.2679	15.8474	37.3976
0.9	31.011	25.5555	37.463

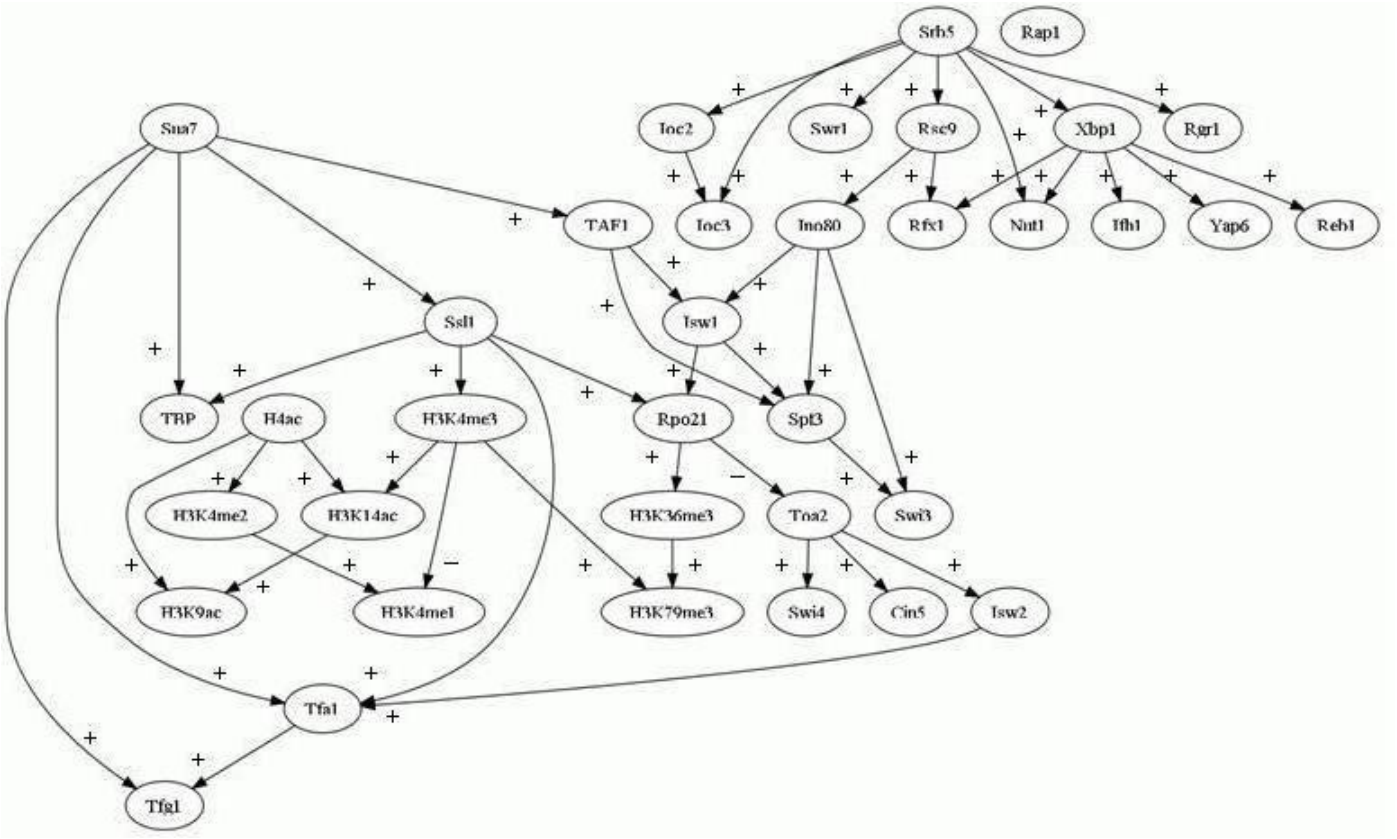

Fig. 1. Bayesian network model of transcriptional relationships. The sign of an edge represents positive(+)/negative(-) influence between two respective nodes.

(Swi3). Among the latter three, Xbp1 and Rfx1 also displayed location-linkage with co-occupying CRCs. These co-occupancy and location-linkage raised the question that whether they reflect the functional relationships among factors or just are the indirect consequence of interactions between those factors with other linked proteins [33]. Our network model provides support for both hypotheses. For example, in the latter four among 6 groups above, all of their members have at least one direct functional linkage to the others in the same group, e.g., $\{Ino80 \rightarrow Isw1, Ino80 \rightarrow Spt3, Ino80 \rightarrow Swi3, Isw1 \rightarrow Spt3, Spt3 \rightarrow Swi3\}$, $\{Sua7 \rightarrow Ssl1, Ssl1 \rightarrow TBP, Sua7 \rightarrow TBP\}$, $\{Rpo21 \rightarrow Toa2\}$, $\{Srb5 \rightarrow Nut1, Srb5 \rightarrow Rgr1\}$. In each of the other two groups, we found only one direct functional linkage, e.g., $\{Ioc2 \rightarrow Ioc3\}$, $\{Tfa1 \rightarrow Tfg1\}$. In comparison with the reported co-occupancy and location-linkage between TFs and CRCs, we found only one strong direct functional linkage $Rsc9 \rightarrow Rfx1$ (with confidence score of 0.969), suggesting that the remaining ones might be the consequence of indirect interactions between those factors with linked proteins (possibly the Mediator).

Among 8 histone modifications in the model, two had direct relationships with transcription machinery, H3K4Me3 and H3K36Me3. H3K4Me3 is a modification related to active chromatin in many eukaryotic organisms [21], [9]. In yeast, tri-methylation of

H3K4 is catalyzed by Set1 methylase, which has been recruited to active regions in chromatin by TFIIH-associated kinase Kin28, a substance phosphorylating the PolII C-terminal domain (CTD) and mediating the transition between initiation and elongation [34]. These relationships were confirmed by our model by the links $TFIIH(Ssl1) \rightarrow H3K4Me3$ and $TFIIH(Ssl1) \rightarrow PolII(Rpo21)$. H3K36Me3 is reported to coincidently appear at MET16 promoter with H3K4Me3 after induction but change quickly after the onset of transcription [31]. Consistent with this observation, the link $PolII(Rpo21) \rightarrow H3K36Me3$ suggests that tri-methylation of H3K36 may be controlled by different mechanism that is also linked with the recruitment and elongation of Pol II.

During transcription, there may be crosstalks among histone modifications [35]. For example, the crosstalk between H3K4Me3 and H3K14Ac in yeast is known to create positive feedback loops in which H3K4Me3 and H3K14Ac may reinforce each other [33]. However, because BN model is limited to the DAG class, our network only presents the link $H3K4Me3 \rightarrow H3K14Ac$. Also, the link $H3K14Ac \rightarrow H3K9Ac$ suggests that H3K14 acetylation by Gcn5 acetyltransferase may cause the acetylation of neibouring domain (H3K9), consistent with the role of Gcn5 in catalyzing these two acetylation events [36].

3.4 Pivotal roles of Mediator, GTFs, and CRCs in trancsriptional regulation

The resulting network contains 3 root nodes, H4Ac, TFIIB (Sua7), and Mediator (Srb5), with corresponding out degrees of 3, 5, and 7 (highest overall the network), confirming the importance of TFIIB, together with other functionally linked GTFs, and Mediator in transcriptional regulation [37], [38], [4].

The network shows that Mediator may impose its effect on transcription through either direct or indirect interactions with remodeling complexes, e.g. RSC (Rsc9), INO80 (Ino80), and ISW1 (Isw1), suggesting the critical roles of these complexes in the process. So far, CRCs are known to translocate or even remove nucleosomes from DNA sequences, by which facilitating the recruitment of Pol II and transcription machinery to the promoter [2], [3]. Their importance in transcription is demonstrated by the fact that some activators are dispensable for maintainance of transcription when nucleosomes are unable to reassemble at a gene promoter [39], [40]. Recent observations on chromatin remodeling activity induced by heat shock at several genes lead to the hypothesis that, instead of acting individually several CRCs may function cooperatively [41], [42], [32]. Taken together with the result from [4], our model provides support for this hypothesis and further suggests that the cooperation of CRCs may be a critical step in genome-wide transcriptional regulation.

One advantage of BN model is that it permits the identification of a group of variables (parents) that combinatorially regulate another one (the common child). In our model, there are two groups of factors cooperatively regulating the recruitment and activity of Pol II (Rpo21), one is GTFs ($Sua7 \rightarrow Ssl \rightarrow Rpo21$), and the other is CRCs ($Srb5 \rightarrow Rsc9 \rightarrow Ino80 \rightarrow Isw1 \rightarrow Rpo21$). Although the importance of GTFs and CRCs in transcriptional regulation have been reported in literature [4], [3], several observations suggested that there may be redundancy in the functions of individual components. For example, the activation of several genes may not need the presence of such critical factors as TFIIA and CTD of Pol II [43], [44]. Our model confirms that, even such redundancy exists, the activities of both GTFs and CRCs are important to transcription, from initiation stage to the onset of elongation. This conclusion is supported by the observation that, even partial PIC had been formed at some genes, PIC is only fully assembled when the -1 nucleosome is removed [45], [4].

4 Conclusion

Transcription in eukaryotic organisms is a complex process requiring the involvement of a large number of proteins, e.g., GTFs, TFs, chromatin remodelers and modifiers. However, their detailed roles as well as how they function together to regulate transcription are still unclear. Using genome-wide mapping data of the transcription machinery and histone modifications from *S.cerevisiae*, we proposed a computational method to reconstruct an unbiased Bayesian network model representing functional relationships among various transcriptional components. Our network model showed high consistency with previous knowledge about their interactions during transcription. A number of novel functional relationships was also suggested, which may bring insights into transcriptional regulation.

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