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A Dynamic Qualitative Probabilistic Network Approach for Extracting Gene Regulatory Network Motifs

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Abstract—This paper extends our work to using qualitative probability to model the naturally-occurring motifs of gene regulatory networks. Having showed in [16] that the qualitative relations defining QPN graphs exhibit a direct mapping to the naturally-occurring network motifs embedded in Gene Regulatory Networks, this work is concerned with generalizing QPN constructs to create a high-level framework from which any regulatory network motif can be derived.

Experimental results using time-series data of the *Saccharomyces Cerevisiae* show the effectiveness of our approach in providing a more accurate description of the regulatory motifs in the *Saccharomyces Cerevisiae* gene regulatory network compared to our previous definitions.

Keywords—Gene Regulatory Networks; Qualitative Probability; Bayesian Learning; Time-series data; Regulatory Network Motifs

I. INTRODUCTION

Network motifs are patterns of interconnections occurring among a small number of nodes (typically three to five) that belong to a large biological network. These motifs are significantly more abundant in real networks than in randomly generated ones, a difference that has been considered to mean that these motifs have been preserved over evolutionary time-scales against mutations that randomly change edges [2], [19]. In gene regulatory networks, these motifs may be considered as the building blocks composing the network because they make up a large component of the overall network structure [19].

Since the discovery of network motifs, a lot of work has been performed to solidify their significance [3], study their structure [2], [19] and establish their evolutionary role [3]. What we are interested in is the establishment of the role of motif discovery in learning the unknown structure of *gene regulatory networks* from microarray data.

Gene regulatory networks model the dynamics of the interactions of genetic information in the cell. In the past years, the problem of finding the structure of these networks from microarray gene expression data has been a focus of studies in systems biology. Having a good model that is capable of predicting the network structure from the data is essential for understanding the working of the cell and is

linked to several applications such as therapeutic targeting, drug design, diagnosis and disease management [1], [15].

In this regard, the past decade has seen many computational models to recover the structure of gene regulatory networks from high-throughput data. Nevertheless, little progress has been made in obtaining meaningful networks containing biologically-relevant relationships [13]. For instance, using Dynamic Bayesian networks for reconstructing gene regulatory networks from microarray expression data [11], [21], [22] generated a lot of promises and research initiatives [13]. However, because of the high dimensionality that characterizes microarray data, any computational model has to search through an exponential number of possible structures before converging to a biologically-sound network model. This, in addition to the ubiquity of noise in microarray data, makes recovering such model a computationally difficult task.

These issues were addressed by the model we developed in [16], [17]. In essence, the idea was to incorporate background knowledge in the form of high-level common-sense information extracted from the data and utilize it to aid the Bayesian algorithm learning the genetic network structure; therefore reducing the search space to only include the models that agree with the background knowledge.

For this, we created *Dynamic Qualitative Probabilistic Networks* (DQPNs) [16], [17], qualitative abstractions of *Dynamic Bayesian Networks*, which are commonly used in gene regulatory network reconstruction [22]. DQPNs replace the conditional probability tables associated with DBNs by qualitative influences, which use signs to encode how the values of probabilities change instead of their exact values. DQPNs have a much faster performance because they do away with the complex computations required to identify conditional dependencies and are therefore valuable in constructing an initial scaffold that a DBN learning algorithm can use to reduce its search space.

In [16], we demonstrated that the qualitative influences defined by DQPNs exhibit a natural mapping to some of the naturally-occurring network motifs of gene regulatory networks. However, DQPN influences are only capable of

representing network motifs where one regulator gene exists for each regulated gene. In this paper, we extend this work by defining a rich model that enables mapping multi-regulator motifs to DQPN influences. We do this by defining a more general notion of DQPN influences and show how it can not only model new motifs but also its ability to better detect single-regulator motifs. Although not part of this paper, the ultimate aim is to use the motifs discovered to present yet another level of background information that the DBN algorithm can use to learn the corresponding genetic network structure.

The rest of the paper is organized as follows. Section II introduces Qualitative Probabilistic Networks (QPNs), which are abstractions of Bayesian Networks. We use QPNs to introduce the notion of an influence, thus establishing the theoretical ground for DQPNs, covered in Section III. In Section III-B, we introduce the new notion of influences capable of modeling any type of genetic network motifs, followed by an experimental analysis comparing the new model to our work in [16] in Section V. The paper concludes by giving a summary and some future directions in Section VI.

II. QUALITATIVE PROBABILISTIC NETWORKS (QPNs)

Qualitative reasoning in probabilistic systems is concerned with building a reasoning engine which makes full use of the principles underlying probabilistic reasoning but captures how probabilities change categorically instead of their exact numerical values [8]. This captured change is modeled by qualitative terms such as increase (+), decrease (-), no change (0) or an unknown change (?) [8]. The idea has been extended to formulate qualitative equivalents of Bayesian networks, termed *Qualitative Probabilistic Networks* (QPNs).

Qualitative Probabilistic Networks (QPNs) are directed acyclic graphs representing qualitative abstractions of Bayesian Networks [8]. They capture the structural properties of Bayesian Network graphs but replace the conditional probability tables by qualitative notions.

Formally, a QPN is given by a pair $G = (V(G), Q(G))$, where $V(G)$ is the set of nodes capturing random variables and $Q(G)$ is the set of arcs capturing the conditional dependence among the variables as in Bayesian Networks. Instead of a known conditional probability distribution however, the arcs of a QPN capture qualitative relations by finding monotonic characteristics in the local conditional probability distribution of each node [8]. The resulting relations are called *qualitative influences* and are used to establish properties over the probabilities of events [8].

Influences describe how the change of the value of a single variable affects that of another, with the effect being categorized as positive, negative, constant or unknown.

A positive influence exists between a parent node X and its child Y (X is said to positively influence Y , written as

$I^+(X, Y)$) if observing higher values for X makes higher values of Y more probable regardless of the value of any other node which may directly influence Y (i.e. any other parent of Y , denoted by W) as given in Definition 1. Negative, constant and unknown influences are analogously defined by replacing the $>$ sign by $<$, $=$ and $?$ respectively.

Definition 1. Positive Influence:

$$I^+(X, Y) \text{ iff } Pr(y|x, W) > Pr(y|\neg x, W)$$

An example of a QPN illustrating influences is given in Figure 1. In the figure, $V(G) = \{\text{Gene A, Gene B, Gene C, Gene D, Gene E}\}$ and $Q(G) = \{(\text{Gene A, Gene D}), (\text{Gene A, Gene C}), (\text{Gene B, Gene C}), (\text{Gene C, Gene E})\}$. The only information encoded in the arcs are the signs of the influences from one node to another extracted from the conditional probability tables of each node. For instance, the negative influence exerted by Gene A on Gene D comes natural from Gene D's conditional probability table given its parent Gene A. Here, W of Definition 1 is the set $\{B\}$ and the sign of the influence is obtained by comparing the probabilities $Pr(c|a, B)$ (which is 1.05) and $Pr(c|\neg a, B)$ (which is 1.0).

Figure 1. A Bayesian Network with the Corresponding QPN

This paper is concerned with using the notion of QPN influences to help discover naturally occurring network motifs in gene regulatory networks. Because QPNs are only used for structure identification, using them for inference will not be discussed here. The interested reader can refer to [8].

III. A DYNAMIC EXTENSION OF QPNs

In [16], we presented Dynamic QPNs (DQPNs) [16] as a temporal extension of QPNs used to qualitatively model a genetic network and their corresponding motifs. In this section, we re-iterate the definition of DQPNs and redefine the notion of qualitative influences for Dynamic QPNs so that they present more flexibility in identifying network motifs. The redefinition is necessary because the binary

nature of the influences (one parent- one child) is not sufficient to define the many-to-many relations occurring in genetic network motifs. Because of this, our work in [16] is only able to define network motifs that contain binary relations and cannot handle multiple interactions.

After presenting DQPNs, we illustrate the notion of a *Generalized Joint Influences* which describe the sought-after many-to-one influences and an algorithm for learning them from expression data. The new formalism is advantageous because it makes the defined the relationship more descriptive of the biological actual model, which will positively impact the quality of the genetic network discovered as experimental studies show.

A. Terminology

Let U be a set of n variables drawn from Pr , an unknown probability distribution on U and let T be a totally ordered set of m temporal slices such that $T_1 \dots T_m \in T$. We denote the set of variables in each temporal slice by U^t ($1 \leq t \leq m$) and the set of n variables in U^t by X_i^t ($1 \leq i \leq n$).

Definition 2. Temporal Snapshot:

Let $G = (V(G), Q(G))$ be a directed acyclic graph (DAG) such that G is the qualitative probabilistic network representing U . An instance G_t of G represents a temporal snapshot of G in time slice T_t such that G_t retains the DAG structure of G .

Figure 2. An Example of G

Example 1. Consider Figure 2 representing a fictitious graph G capturing the I-map for Pr , the joint probability distribution on $U = \{A_1, A_2, A_3, A_4\}$. Each instance G_t of G ($1 \leq t \leq 3$ in the figure) represents a snapshot of G , where the variables in each temporal slice are given by $U_t = \{A_1^t, A_2^t, A_3^t, A_4^t\}$.

Definition 3. Dynamic Instance:

Let G_t be as given in definition 2. G_t defines a dynamic instance of the QPN whose structure is defined by G and is given by $G_t = (V(G_t), \{Q(G_t) \cup T(G_t)\})^1$, where $V(G_t)$ and $Q(G_t)$ are instances of $V(G)$ and $Q(G)$ respectively at time slot t , and $T(G_t)$ describes the inter-slot conditional

¹For readability purposes, we will refer to $\{Q(G_t) \cup T(G_t)\}$ as $\Omega(G_t)$ in this work.

dependence between variables in $V(G_t)$ and its immediate neighbor $V(G_{t+1})$.

Example 2. In the graph given in Figure 2, for each G_t , $V(G_t) = U_t$, $Q(G_t) = \{(A_1^t, A_3^t), (A_2^t, A_3^t), (A_3^t, A_4^t), (A_2^t, A_4^t)\}$ and $T(G_t) = \{(A_4^t, A_{t+1}^{t+1})\}$.

Both of $Q(G)$ and $T(G)$ encode a set of arcs for G to capture the set of qualitative relations representing how variables influence each other. For this, we redefine the concept of a qualitative influence to capture not only within-slot relations, but also inter-slot ones. Before doing so however, we first present the definition of a *Dynamic Qualitative Probabilistic Network* (DQPN) below.

Definition 4. Dynamic QPN:

Let $(G_1 = (V(G_1), \Omega(G_1)), \dots, G_m = (V(G_m), \Omega(G_m)))$ be a total ordering of the m instances of G such that $T(G_t) \neq \emptyset$, $\forall 1 \leq t \leq m-1$. Then the compound graph of $G_1, \dots, G_m$ defines a *Dynamic Qualitative Probabilistic Network* over G and is given by

$$\bigcup_{t=1}^m G_t = (\bigcup_{t=1}^m V(G_t), \bigcup_{t=1}^m \Omega(G_t))$$

B. Qualitative Influences in a DQPN

In contrast to QPNs and the definition of DQPNs we give in [16], we define here *Generalized joint influences* as the basic constructs making up DQPN interactions. Essentially, of a set of k variables $X_1, \dots, X_k$ over a target variable Y which describes the monotonic relationship between the values of the variables $X_1, \dots, X_k$ jointly and that of Y . Definition 5 below illustrates a positive generalized joint influence $J^+(\{X_1, \dots, X_k\}, Y)$. In the definition, the superscript i denotes the time-slots at which the value of the child node y is observed while the superscripts $j_1, \dots, j_k$ denote the time-slots at which the influencing parents $X_1, \dots, X_k$ are observed.

Definition 5. Positive Generalized Joint Influence

$J^+(\{X_1, \dots, X_k\}, Y)$ iff for value y of Y observed at time-slot i and for any combination of values for variables $X_1, \dots, X_k$ observed at time-slots $j_1, \dots, j_k$ such that $j_1, \dots, j_k \leq i$:

$$Pr(y^i | x_1^{j_1}, W) > Pr(y^i | \neg x_1^{j_1}, W)$$

when $k = 1$

$$Pr(y^i | x_1^{j_1}, \dots, x_k^{j_k}, W) + Pr(y^i | \neg x_1^{j_1}, \dots, \neg x_k^{j_k}, W) > \wp$$

when $k > 1$

Where $\wp$ is the difference between the conditional probabilities of Y given any combination of values for $X_1, \dots, X_k$ other than $x_1^{j_1}, \dots, x_k^{j_k}$ and $\neg x_1^{j_1}, \dots, \neg x_k^{j_k}$.

The definition enforces a temporal order over its components by requiring that variables can only directly influence

other variables that belong to a similar or a preceding temporal slot ($j_1, \dots, j_k \leq i$). Moreover, it can be seen that the case of influences can be directly extracted from the definition by setting $k = 1$ and that negative and zero joint generalized influences can be analogously defined by replacing $>$ by $<$ and $=$ respectively.

In our next steps, we will use generalized joint influences of DQPNs to guide the process of discovering network motifs in gene regulatory networks. The motifs to be discovered are shown in Figure 3 and are the feed-forward motifs and the multi-input motif, which is a generalization of the bi-fan motif (also shown in the figure). When referencing the influences defined above, we will use the notation $J^e(\{X_1, \dots, X_k\}, Y)$ where $e \in \{+, -, 0\}$.

Figure 3. (a) The Bi-fan Motifs (b) The Feed-forward loop motifs (c) The Multi-input motif. The orange circles represent genes and the arcs represent regulatory relations.

IV. MOTIF MODELING USING DQPNs

The definition of a Generalized Joint Influence introduced in the previous section models regulatory relations between a number of regulators and a regulated genes. As a result, defining the motifs given in Figure 3 is directly obtained from the constructs of the DQPN as given in definitions 6 - 8.

Definition 6. Feed-forward loops

A feed-forward loop exists in a genetic network modeled by a DPQN defined over G iff for three genes $X_{i_1}^{j_1}$, $X_{i_2}^{j_2}$, $X_{i_3}^{j_3}$:

$$J^{\delta_1}(\{X_{i_1}^{j_1}\}, X_{i_2}^{j_2}) \wedge J^{\delta_2}(\{X_{i_2}^{j_2}\}, X_{i_3}^{j_3}) \wedge J^{\delta_3}(\{X_{i_1}^{j_1}\}, X_{i_3}^{j_3})$$

Where i_1, i_2, i_3 are the time-slots where the genes are active; the subscripts denote the different genes. Also, the regulator gene should be expressed prior to the regulated gene, hence: $i_1 \leq i_2 \leq i_3$

Where $\delta_1, \delta_2 \in \{+, -, ?, 0\}$. The above definition states that a feed-forward loop exists if a gene regulates another via two different trails.

Definition 7. Bi-fans

A bi-fan motif of two genes $X_{k_1}^{i_1}$ and $X_{k_2}^{i_2}$ on two other genes $X_{l_1}^{j_1}$ and $X_{l_2}^{j_2}$ exists in a genetic network modeled by a DPQN defined over G iff:

$$J^{\delta_1}(\{X_{k_1}^{i_1} \wedge X_{k_2}^{i_2}\}, X_{l_1}^{j_1}) \wedge J^{\delta_2}(\{X_{k_1}^{i_1} \wedge X_{k_2}^{i_2}\}, X_{l_2}^{j_2})$$

Where $\delta_1, \delta_2 \in \{+, -, ?, 0\}$, i_1, i_2 are the time-slots to which the regulators belong, j_1, j_2 are the time-slots to which the regulated genes belong and $i_1, i_2 \leq j_1, j_2$.

Definition 8. Multi-input Motif

A multi-input motif of a set of n genes $X_{k_1}^{i_1}, \dots, X_{k_n}^{i_n}$ on m other genes $X_{l_1}^{j_1}, \dots, X_{l_m}^{j_m}$ exists in a genetic network modeled by a DPQN defined over G iff:

$$\forall a \in \{1, \dots, m\} : J^{\delta}(\{X_{k_1}^{i_1} \dots X_{k_n}^{i_n}\}, X_{l_a}^{j_a})$$

Where $\delta \in \{+, -, ?, 0\}$, $i_1, \dots, i_n$ are the time-slots to which the regulators belong, $j_1, \dots, j_m$ are the time-slots to which the regulated genes belong and $i_1, \dots, i_n \leq j_1, \dots, j_m$.

V. EXPERIMENTAL ANALYSIS

We conducted a set of experiments to compare the performance of the generalized joint influences versus that of the original binary influences given in [16] in defining and discovering the desired motifs. This comparison is done using the following steps:

- 1) Use binary influences to define the feed-forward motif.
- 2) Use generalized joint influences to define the feed-forward motif.
- 3) Compare the number of motifs discovered in both cases and the overall monotonicity of the number of motifs to the size of the network.
- 4) Repeat steps 1 - 3 for bi-fan motifs.
- 5) Repeat steps 1 - 3 for multi-input motifs.

We conducted a set of experiments to test the hypothesis of whether or not the added generalization has a positive effect on the number of motifs detected. The data set used for the purpose is based on the YPD (Yeast protein database) (S2) and was obtained from the data set used in

Table I

NODES = NUMBER OF NODES (GENES) IN THE RUN, $EDGE_{avg}$ = AVERAGE NUMBER OF EDGES FOR 10 RUNS OF NETWORKS OF SIZE N
 FEED-FORWARD = AVERAGE NUMBER OF FEED-FORWARD MOTIFS FOR THE 10 RUNS USING BINARY INFLUENCES, BI-FAN = AVERAGE NUMBER OF BI-FAN MOTIFS FOR THE 10 RUNS USING BINARY INFLUENCES
 $FEED-FORWARD_G$ = AVERAGE NUMBER OF FEED-FORWARD MOTIFS FOR THE 10 RUNS USING GENERALIZED JOINT INFLUENCES, $BI-FAN_G$ = AVERAGE NUMBER OF BI-FAN MOTIFS FOR THE 10 RUNS USING GENERALIZED JOINT INFLUENCES

Nodes	$EDGE_{avg}$	Feed-forward	Bi-fan	$FEED-FORWARD_G$	$BI-FAN_G$
85	154	16	209	28	312
185	372	18	430	27	534
285	518	21	825	35	887
385	698	29	1092	32	1413
485	912	46	1437	39	1576
585	997	52	1745	52	1925

Table II

THE RESULTS WITH RESPECT TO THE NUMBER OF MULTI-FAN MOTIFS

Nodes	$EDGE_{avg}$	Multi-fan	$Multi-fan_G$
85	154	12	11
185	372	16	21
285	518	23	41
385	698	78	98
485	912	131	230
585	997	144	301

[19] and contains 1079 interactions of 688 genes describing the regulation relationships of the transcriptional regulatory network of *Saccharomyces Cerevisiae*. The data set is the same as the one used in [16], however, the interactions are labeled by subscripts describing the time-point at which the gene is activated. For example, a row in the database such as $g1_{t1}, g2_{t2}$ describes an interaction between genes $g1$ and $g2$ such that $g1$ regulates $g2$ and $g1$ is activated in time point $t1$ and $g2$ is activated in time point $t2$. The data comprises of three columns representing regulating genes, regulated genes and the mode of regulation. The results are summarized in table I.

The table shows that the number of motifs discovered using generalized joint influences exceeds the ones discovered using binary influences for the three types of motifs. While this maybe expected for the bi-fan and multi-input motifs, it may come as surprising for the feed-forward motif.

Upon close examination however, it turns out that the relaxed definition of temporal precedence for generalized joint influences has something to do with it. More specifically, generalized joint influences, unlike binary influences, do not require both the regulator and regulated genes to be in two consecutive time-slots and merely require that the regulator gene be on an earlier time-slot than the regulated gene as definition 5 shows. This has helped discover many of the interactions that did not adhere to the consecutive constraint

of binary influences and therefore helped in discovering more network motifs. Hence, the refined qualitative model is deemed more suitable for modeling genetic interactions than the original QPNs and DQPNs.

VI. CONCLUSIONS AND FUTURE RESEARCH

We presented the notion of a Generalized Joint Influence, a qualitative relation capable of defining regulatory relations in gene regulatory networks. The relation is based on conditional dependence and is used to define qualitative equivalents of Dynamic Bayesian Networks.

We use the relationship to define three motifs commonly occurring in the gene regulatory network of *Saccharomyces Cerevisiae*, mainly the feed-forward motif, the bi-fan motif and the multi-input motif. The experimental results show that Generalized Joint Influences are better suited than the classic notion of influences in modeling gene regulation as they detect more biologically relevant motifs.

The next step is to use the motifs constructed as a platform to aid a DBN-based learning algorithm for constructing gene regulatory networks from microarray gene expression data.

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