Relationships Between Probabilistic Boolean Networks and Dynamic Bayesian Networks as Models of Gene Regulatory Networks

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- ▷ Discrete Network Models: PBNs and DBNs
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- ▷ Further Topics

Background/Motivation

- ▷ Discrete gene regulatory network models.
- ▷ Coarse-scale models emphasize fundamental, generic principles between interacting components.
- ▷ The currently available data is limited both in quality and the number of samples.
- ⇝ There may not be big advantage using models that are much more accurate than the currently available data.
- ▷ Also, the modeling framework should be selected on the basis of the preferred goals.
- ⇝ Do we want to model the generic principles or the biochemical details?

Background/Motivation (2)

- Discrete gene regulatory network models have some obvious limitations as well. . .
- The frequently used coarse-scale network models are:
  - Boolean Networks,
  - Probabilistic Boolean Networks (PBN), and
  - Dynamic Bayesian Networks (DBN).

Background/Motivation (3)

- **Motivation:** Advanced analysis tools have been developed for both PBNs and DBNs.
- **Goal:** Show certain relationships between the PBNs and a subclass of DBNs — they can represent the same probability distributions.
- **Benefits:** That opens up the possibility of applying the standard tools of DBNs to PBNs and vice versa.

  In other words, the introduced relationships between the models extend the collection of analysis tools for both model classes.

Network Models — PBNs

- A PBN $G(V, F)$ is defined by a set of binary-valued nodes $V = \{X_1, \ldots, X_n\}$ and a list of Boolean function sets $F = (F_1, \ldots, F_n)$, where $F_i = \{f_1^{(i)}, \ldots, f_{l(i)}^{(i)}\}$.
- The value of each node X_i is updated by a Boolean function taken from the corresponding set F_i.

Network Models — PBNs (2)

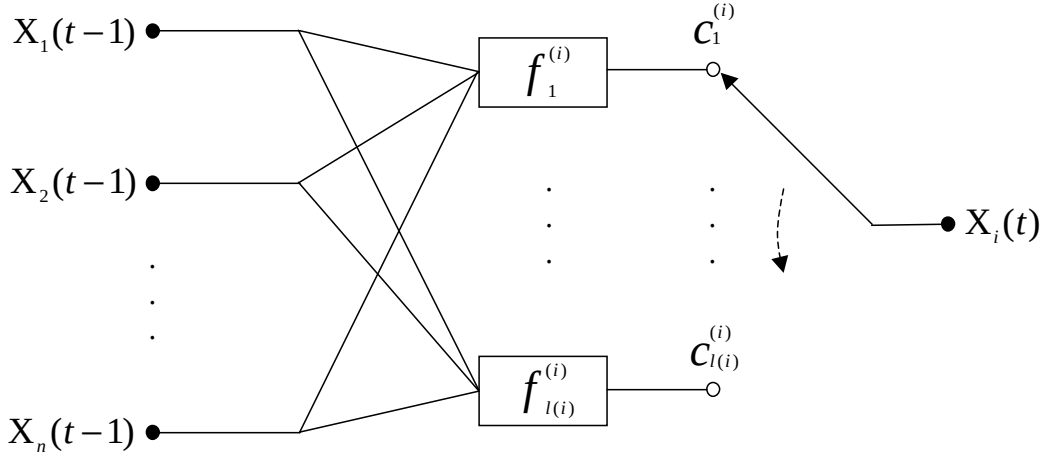


Figure 1: A basic building block of an independent PBN.

Network Models — PBNs (3)

- A realization of the PBN at a given time instant is defined by a vector of Boolean functions

$$\mathbf{f}_j = (f_{j_1}^{(1)}, \ldots, f_{j_n}^{(n)}).$$

- Thus, $\mathbf{f}_j : \{0,1\}^n \to \{0,1\}^n$.
- Let $\mathbf{X}(t) = (X_1(t), \ldots, X_n(t))$.
- The updating step from time $t-1$ to t is

$$\mathbf{x}(t) = \mathbf{f}_j(\mathbf{x}(t-1)).$$

Network Models — PBNs (4)

- The realizations are selected randomly (and independently for each time instant) from a pdf

$$\Pr\{\mathbf{F} = \mathbf{f}\}.$$

- A PBN is said to be independent if

$$\Pr\{\mathbf{F} = \mathbf{f}\} = \prod_{i=1}^{n} \Pr\{F^{(i)} = f^{(i)}\}.$$

Network Models — PBNs (5)

- ▷ Dynamics of PBNs can be studied using Markov Chains.
- ▷ Given the initial state $\mathbf{x}(t-1)$, the probability of moving to some state $\mathbf{x}(t)$ after one step of the network is

$$A(\mathbf{x}(t-1),\mathbf{x}(t)) = \sum_{j\,:\,\mathbf{f}_j(\mathbf{x}(t-1))=\mathbf{x}(t)} \Pr\{\mathbf{F}=\mathbf{f}_j\}.$$

- ▷ For independent PBNs

$$A(\mathbf{x}(t-1),\mathbf{x}(t)) = \prod_{i=1}^{n} A(\mathbf{x}(t-1),(\mathbf{x}(t))_i).$$

Network Models — DBNs

- A Bayesian Network (BN) for a set of (binary) variables $\mathbf{X} = \{X_1, \ldots, X_n\}$ is a pair $B = (G, \Theta)$.
  - G is a directed acyclic graph.
  - Θ defines a set of local conditional probability distributions.
- A BN B defines a unique joint probability distribution over $\mathbf{X}$ given by

$$\Pr\{x_1, \ldots, x_n\} = \prod_{i=1}^{n} \Pr\{x_i | \mathbf{pa}(X_i)\}.$$

Network Models — DBNs (2)

- We are interested in the joint probability distribution of the variables expanded over a finite number of updating steps,

$$\{\mathbf{X}(0), \mathbf{X}(1), \ldots, \mathbf{X}(T)\}.$$

- A Dynamic Bayesian Network (B_0, B_1) consists of two parts:
  - An initial BN $B_0 = (G_0, \Theta_0)$ that defines the joint distribution of the variables in $\mathbf{X}(0)$, and
  - A transition BN $B_1 = (G_1, \Theta_1)$ that specifies the transition probabilities $\Pr\{\mathbf{X}(t)|\mathbf{X}(t-1)\}$ for all $t > 0$.

Network Models — DBNs (3)

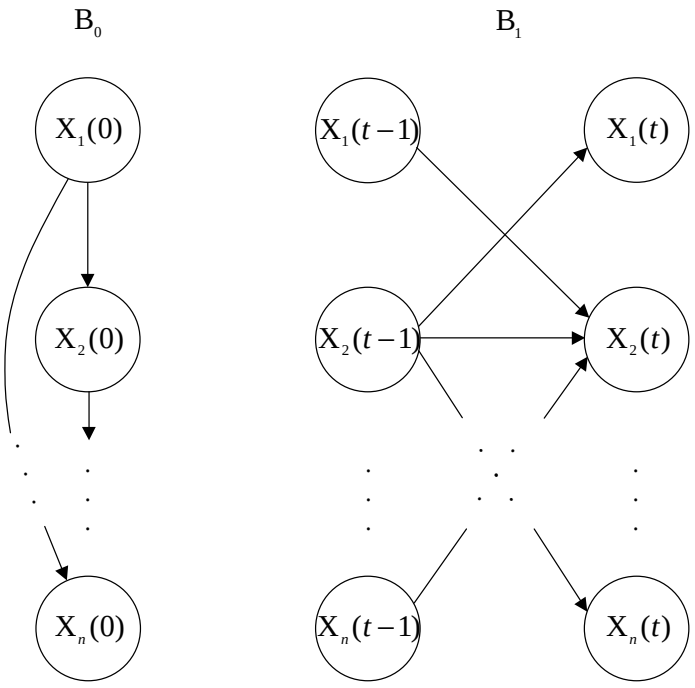


Figure 2: The basic building blocks of DBNs.

Network Models — DBNs (4)

- Constraints:
  - Nodes are binary-valued,
  - G_0 is assumed to have only within-slice connections,

$$\mathbf{Pa}(X_i(0)) \subseteq \mathbf{X}(0), \text{ for all } 1 \leq i \leq n,$$

  - Variables in time slice $t > 0$, have all their parents in slice $t - 1$,

$$\mathbf{Pa}(X_i(t)) \subseteq \mathbf{X}(t-1) \text{ for all } 1 \leq i \leq n.$$

Relationships Between the Models

▷ For the independent PBNs:

$$\begin{aligned}&\Pr\{\mathbf{X}(0)=\mathbf{x}(0),\ldots,\mathbf{X}(T)=\mathbf{x}(T)\}\\&=\Pr\{\mathbf{X}(0)=\mathbf{x}(0)\}\prod_{t=1}^{T}\left(\prod_{i=1}^{n}A(\mathbf{x}(t-1),(\mathbf{x}(t))_i)\right).\end{aligned}$$

▷ For the DBNs:

$$\begin{aligned}&\Pr\{\mathbf{x}(0),\mathbf{x}(1),\ldots,\mathbf{x}(T)\}\\&=\Pr\{\mathbf{x}(0)\}\prod_{t=1}^{T}\prod_{j=1}^{n}\Pr\{x_j(t)|\mathbf{pa}(X_j(t))\}.\end{aligned}$$

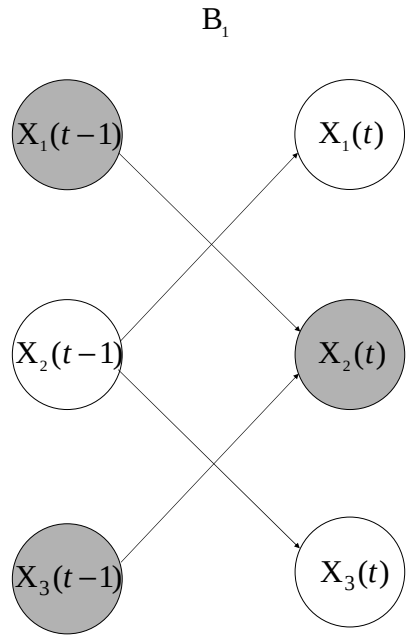
Relationships Between the Models(2)

- An independent PBN as a DBN:
  - G_1: parents of X_i are all the input variables of the functions in F_i.
  - Θ_1:

$$\Pr\{X_i(t) = 1 | \mathbf{Pa}(X_i(t)) = \mathbf{z}\} = \sum_{j=1}^{l(i)} f_j^{(i)}(\mathbf{z}) c_j^{(i)}.$$

Relationships Between the Models(3)

- ▷ A binary-valued DBN as an independent PBN:
- ▷ Example: consider e.g. node X_2.



Relationships Between the Models(4)

$\mathbf{y}$	z	$\Pr\{X_2(t) = z \mid \mathbf{Pa}(X_2(t)) = \mathbf{y}\}$
00	1	0.2
01	1	0.6
10	1	0.7
11	1	0.75

$f_j^{(2)}$	$c_j^{(2)}$
$f_1^{(2)} = \overline{x}_1\overline{x}_3 \vee \overline{x}_1 x_3 \vee x_1\overline{x}_3 \vee x_1 x_3$	$c_1^{(2)} = 0.2$
$f_2^{(2)} = \overline{x}_1 x_3 \vee x_1\overline{x}_3 \vee x_1 x_3$	$c_2^{(2)} = 0.6 - 0.2 = 0.4$
$f_3^{(2)} = x_1\overline{x}_3 \vee x_1 x_3$	$c_3^{(2)} = 0.7 - 0.6 = 0.1$
$f_4^{(2)} = x_1 x_3$	$c_4^{(2)} = 0.75 - 0.7 = 0.05$
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Relationships Between the Models(5)

- **Theorem 1.** Independent PBNs $G(V, F)$ and binary-valued DBNs (B_0, B_1) whose initial and transition BNs B_0 and B_1 are assumed to have only within and between consecutive slice connections, respectively, can represent the same joint distribution over their common variables.
- One can show similar relationships between dependent PBNs and discrete-valued DBNs.

Relationships Between the Models(6)

▷ **Theorem 2.** Dependent PBNs $G(V, F)$ and discrete-valued DBNs (B_0, B_1) whose initial and transition BNs B_0 and B_1 are assumed to have only within and between consecutive slice connections, respectively, can represent the same joint distribution over their corresponding variables.

Benefits of the Relationships

- Tools that can be used for DBNs.
  - Tools for controlling the stationary behavior of PBNs by means of
    - interventions,
    - structural modifications of the network, and
    - optimal external control.
  - ⇝ This is the ultimate goal (e.g. drug design).
  - Efficient learning schemes.
  - Mappings between different networks, such as projections onto subnetworks.
  - ⇝ Often necessary in practise due to large number of genes.

Benefits of the Relationships (2)

- Tools that can be used for PBNs.
  - Standard learning tools of DBNs.
  - ⇝ Efficient and flexible tools, with a possibility to be able to combine different data sources, are needed!
  - Both exact and approximate inference tools.
  - ⇝ Give a natural way of handling the missing values in PBNs which are often present in gene expression measurements.

Benefits of the Relationships (3)

- Tools that can be used for PBNs (continues).
  - Greedy active learning methods for Bayesian Networks.
  - ⇝ Design the experiments in order to gain maximal advantage.
  - ⇝ The use of active learning can remarkably reduce the number of measurements required to learn the model.

Further Topics

- Different information sources can be used in a principled way in the DBN model inference.
- The optimal DBN model structures maximize the a posteriori probability of the model

$$\Pr\{\mathcal{M}|\mathcal{D}\} \propto \Pr\{\mathcal{D}|\mathcal{M}\}\Pr\{\mathcal{M}\}.$$

- Incorporate more additional information sources into the learning process through $\Pr\{\mathcal{M}\}$.
  - Protein-DNA binding data, sequence data, a priori knowledge, protein-protein interactions, etc.

Further Topics (2)

▷ Another interesting implication can be seen after rewriting $\Pr\{\mathcal{M}|\mathcal{D}\}$ as

$$\Pr\{\mathcal{M}|\mathcal{D}\} \propto \left(\int \Pr\{\mathcal{D}|\mathcal{M},\theta\}\Pr\{\theta|\mathcal{M}\} \right) \Pr\{\mathcal{M}),$$

where $\Pr\{\theta|\mathcal{M}\}$ denotes the parameter prior.

▷ The parameters in DBNs correspond to the predictor functions and their selection probabilities in PBNs.

⇝ One can also use the natural constraints of the predictor function classes (e.g. canalizing and Post functions) in the learning phase in a Bayesian fashion.

Further Topics (3)

- For instance, canalizing and Post function classes are found to have biological motivation and provide some desirable properties.
- One can also assess the plausibility of different function classes in gene regulatory network modeling by examining their prediction capabilities.
- One is interested in cost of constraint

$$\Delta_{\mathcal{C}_k} = \epsilon_{\cdot}(\mathcal{C}_k) - \epsilon_{\cdot}(\mathcal{F}_k)$$

Further Topics (4)

- ▷ Assuming the function classes of interest are really representative, e.g., the underlying binary system is governed by one of the classes, say $\mathcal{C}_k$, then $\Delta_{\mathcal{C}_k} = 0$.
- ⇝ The question to be answered is that whether the cost of constraint is statistically significant.

Conclusion

- ▷ Of the primary interest were the relationships between Dynamic Bayesian Networks and Probabilistic Boolean Networks.
- ⇝ As the theory of both DBNs and PBNs is under vigorous research, new advances are directly applicable to the gene regulatory networks under both models.