Inference of Restricted Stochastic Boolean GRN's by Bayesian Error and Entropy Based Criteria

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Abstract. This work compares two frequently used criterion functions in inference of gene regulatory networks (GRN), one based on Bayesian error and another based on conditional entropy. The network model utilized was the stochastic restricted Boolean network model; the tests were realized in the well studied yeast cell-cycle and in randomly generated networks. The experimental results support the use of entropy in relation to the use of Bayesian error and indicate that the application of a fast greedy feature selection algorithm combined with an entropy-based criterion function can be used to infer accurate GRN's, allowing to accurately infer networks with thousands of genes in a feasible computational time cost, even though some genes are influenced by many other genes.

Keywords: feature selection, gene regulatory networks inference, stochastic restricted Boolean network models, entropy, Bayesian error.

1 Introduction

Gene regulatory networks (GRN) models help us to study biological phenomena (e.g. cell cycle) and diseases (e.g. cancer). Therefore, the inference of such networks is an important problem to be addressed. Unfortunately, the GRN inference problem usually involves data with a large number of variables and small number of observations, making the problem particularly hard due to error estimation issues. In this context, many inference algorithms have been proposed. A survey of GRN inference methods can be found in [1].

In this context, we compare two feature selection criteria commonly used for inference of gene regulatory networks, one based on Bayesian error (non-linear coefficient of determination) and another based on mean conditional entropy (uncertainty coefficient). The experiments considered the stochastic model of the yeast cell cycle provided by Zhang *et al*, which is based on restricted Boolean networks [2]. Besides the network topology of the yeast cell cycle model, other randomly generated topologies following a similar parametrization were included

in the experiments. Applying exhaustive search and a classical and fast feature selection algorithm (Sequential Forward Selection - SFS) to the transition matrices corresponding to such networks, it can be observed a significantly better performance of the entropy over the Bayesian error in recovering the groundtruth connections. Besides, the application of SFS guided by the entropy based criterion led to surprisingly good results, which is a valid alternative to become feasible the inference of GRNs considering thousands of genes with nice quality. These findings are the main contribution of this work.

Next section presents a brief background on feature selection, the algorithms and criterion functions used. In Section 3, the restricted Boolean network model of the yeast cell-cycle is presented. Section 4 discusses the GRN inference results obtained by the application of the considered algorithms criterion functions. Finally, the conclusion of this work along with future perspectives are found in Section 5.

2 Feature Selection

Feature selection techniques are composed by two main parts: a search algorithm and a criterion function that guides the algorithm. In feature selection, the only way to guarantee that the optimal solution be achieved is by exploring all possible subsets of all dimensions (exhaustive search), although depending on the behavior of the criterion function, it is possible to design branch-and-bound algorithms that obtain the optimal solution without the need to investigate the whole space of solutions [3, 4]. Greedy algorithms like Best Individual Features or Sequential Forward Selection (SFS) are very fast, although do not guarantee the optimal solution due to the *nesting effect*, i.e. a phenomenon in which the inclusion of the best features according to a given criterion may not lead to the optimal subset [5]. Yet, this phenomenon can be explained by the intrinsically multivariate prediction concept [6], also known as synergy [7], which states that it is possible to obtain a very good predictor set with regard to a considered target even that all its properly contained subsets do not offer any prediction about the target. Due to the nesting effect, many floating search algorithms that try to alleviate it by trying to successively add elements to and remove elements from the current solution have been proposed.

Here the attention is given to the SFS, a genuinely greedy feature selection algorithm [8]. It starts with the empty set and includes the best feature according to the criterion function. In every step i , it adds the i -th feature that forms the best set with the already included $i - 1$ features in the partial solution. This process continues until reaching a stop condition, which usually either is based on a fixed dimensionality given as input or based on the evaluation of the improvement of the criterion function (if the improvement by adding the next feature is smaller than a certain threshold, it stops).

With regard to the criterion functions, the focus is given on two commonly used criteria in GRN inference. One of them is the coefficient of non-linear determination (CoD), which considers the error committed by a subset in classifying

the target value (Bayesian error) [9, 10, 11]. The CoD of the target Y given the knowledge of $\mathbf{X} = (X_1, \dots, X_n)$ is given by:

$$CoD_Y(\mathbf{X}) = \frac{\varepsilon(Y) - \varepsilon(Y|\mathbf{X})}{\varepsilon(Y)} \quad (1)$$

where $\varepsilon(Y) = 1 - \max_{y \in Y} P(y)$ is the prior error, i.e. the error by predicting Y in the absence of other observations, and $\varepsilon(Y|\mathbf{X}) = \sum_{\mathbf{x} \in \mathbf{X}} P(\mathbf{x})(1 - \max_{y \in Y} P(y|\mathbf{x}))$ is the average error by predicting Y based on the observation of $\mathbf{X}$.

Criterion functions based on entropy (H), such as mutual information or mean conditional entropy, are frequently adopted for GRN inference as well [12, 13]. The Uncertainty Coefficient (UC) is similar to CoD, but instead of using Bayesian error, it employs entropy [14]. Its equation is given by:

$$UC_Y(\mathbf{X}) = \frac{H(Y) - H(Y|\mathbf{X})}{H(Y)} \quad (2)$$

where $H(Y) = -\sum_{y \in Y} P(y) \log P(y)$ is the entropy of predicting Y in the absence of other observations, and $H(Y|\mathbf{X}) = \sum_{\mathbf{x} \in \mathbf{X}} P(\mathbf{x}) H(Y|\mathbf{x})$ is the mean conditional entropy of Y given the observation of $\mathbf{X}$.

3 Yeast Cell-Cycle Stochastic Restricted Boolean Model

Following the yeast cell-cycle model with 11 genes proposed by Li *et al* [15] and its stochastic version [2], a *Restricted Boolean Network* is defined as a graph where each node is represented by a Boolean variable $s_i \in \{0, 1\}$ and its dynamics is given by the following transition probabilities:

$$P(s_1(t+1), s_2(t+1) \dots s_{11}(t+1) | s_1(t), s_2(t) \dots s_{11}(t)) = \prod_i P(s_i(t+1) | s_1(t), s_2(t) \dots s_{11}(t)), \quad (3)$$

where

$$P(s_i(t+1) = \sigma_i | s_1(t), \dots, s_{11}(t)) = \frac{\exp\{-\beta(1 - 2\sigma_i) \sum_j w_{ij} s_j\}}{\exp\{-\beta \sum_j w_{ij} s_j\} + \exp\{\beta \sum_j w_{ij} s_j\}}, \quad (4)$$

if $\sum_j w_{ij} s_j \neq 0$ or

$$P(s_i(t+1) = s_i(t) | s_1(t), \dots, s_{11}(t)) = 1/(1 + \exp\{-\alpha\}) \quad (5)$$

otherwise.

In the context of gene regulatory networks, $s_i(t)$ represents the expression of gene i at the moment t ; w_{ij} sets the influence of gene i on gene j ($w_{ij} \in \{-1, 0, 1\}$ for $i \neq j$ and $w_{ij} \in \{-0.1, 0\}$ for $i = j$). The parameters α and β are positive and related to intrinsic and input noises, respectively. They work as inverse temperatures, i.e. the probability of the system to follow the deterministic pathway increases with their values. These deterministic pathways are the trajectories of the system in the state space of the noiseless case. In the Zhang *et al* model,

these pathways are the trajectories of the network state in the deterministic yeast cell-cycle model [15].

For a network with N nodes, there are 2^N distinct states. Naturally, some of these states are not allowed in the dynamics of the deterministic model (noiseless case). But in the presence of noise, the system eventually can be found in some of the “forbidden” states.

The model proposed by Equations 4 and 5 comes from the assumption in which all nodes are under the same kind of noise and that the transition function does not change in time, which means that it is a time homogeneous Markovian process. Besides, as can be noted, all states are accessible, *i.e.* the Markov chain is ergodic and, therefore, there is a time-invariant probability distribution $\pi = (\pi_0, \pi_1, \dots, \pi_{2^N-1})$ to which the system converges:

$$\lim_{r \rightarrow \infty} p_{mn}(r) = \pi_n, \quad 0 \leq m, n < 2^N \quad (6)$$

where $p_{mn}(r)$ is the element on the row m and column n of P^r , with P being the transition matrix defined by Eq. 3.

4 Experimental Results

Using the model described in Section 3, we have all state transition probabilities of the Markov chain process given in a matrix P . As this is an ergodic matrix (see Section 3), we have the limit probability distribution of all states given by the vector π . With P and π , it is possible to obtain the joint probability distribution table (JPD) for all possible subsets of variables, allowing to apply criterion functions to evaluate any subset of genes as predictor candidates for any gene considered as target [16].

Here we considered two feature selection algorithms: the exhaustive search (which examines all possible subsets of all dimensions, returning the optimal subset with the smallest dimension) and the SFS (see Section 2 for a brief description) with a stop condition that is based on the improvement of the criterion (if the addition of the n -th gene does not improve the result obtained by the current subset of dimension $n - 1$, the process returns the last one as result). Each algorithm was applied considering two criterion functions: CoD (Bayesian error based, see Equation 1) and UC (entropy based, see Equation 2). Therefore, four methods were considered for comparison: exhaustive search with CoD (ES-CoD), exhaustive search with UC (ES-UC), SFS with CoD (SFS-CoD) and SFS with UC (SFS-UC).

In the first experiment, we set the w_{ij} 's as the Zhang *et al* model [2] and applied the four methods aforementioned to the inference of the network in the case of small ($\alpha = 5, \beta = 6$) and large temperature ($\alpha = 0.05, \beta = 0.06$). The accuracy was perfect in both cases, *i.e.* the network was fully recovered, presenting neither false positives nor false negatives for all methods used (ES-CoD, ES-UC, SFS-CoD and SFS-UC).

In order to compare the inference performance obtained by the CoD and the UC criteria in more situations, we generate random networks with a parametrization close to that presented by the cell-cycle network of the budding yeast using

Table 1. Tables containing the numbers of false negatives (FN) and false positives (FP) obtained by the application of ES-CoD, ES-UC, SFS-CoD and SFS-UC to infer each one of the 10 randomly generated topology samples considering small temperature ($\alpha = 5, \beta = 6$) and large temperature ($\alpha = 0.05, \beta = 0.06$).

		Sample 1								Sample 2							
		ES-CoD		ES-UC		SFS-CoD		SFS-UC		ES-CoD		ES-UC		SFS-CoD		SFS-UC	
α	β	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP
5	6	12	0	3	0	12	0	3	0	0	0	0	0	7	0	0	1
0.05	0.06	0	0	0	0	12	0	0	0	0	0	0	0	17	0	0	0

		Sample 3								Sample 4							
		ES-CoD		ES-UC		SFS-CoD		SFS-UC		ES-CoD		ES-UC		SFS-CoD		SFS-UC	
α	β	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP
5	6	3	0	0	0	8	0	0	0	0	0	0	0	3	0	0	0
0.05	0.06	3	0	0	0	17	0	0	0	0	0	0	0	20	0	0	0

		Sample 5								Sample 6							
		ES-CoD		ES-UC		SFS-CoD		SFS-UC		ES-CoD		ES-UC		SFS-CoD		SFS-UC	
α	β	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP
5	6	0	0	0	0	8	0	0	1	1	0	0	0	12	0	0	0
0.05	0.06	0	0	0	0	18	0	0	0	0	0	0	0	18	0	0	0

		Sample 7								Sample 8							
		ES-CoD		ES-UC		SFS-CoD		SFS-UC		ES-CoD		ES-UC		SFS-CoD		SFS-UC	
α	β	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP
5	6	14	0	11	0	17	0	11	0	0	0	0	0	2	0	0	0
0.05	0.06	0	0	0	0	22	0	0	0	4	0	0	0	9	0	0	0

		Sample 9								Sample 10							
		ES-CoD		ES-UC		SFS-CoD		SFS-UC		ES-CoD		ES-UC		SFS-CoD		SFS-UC	
α	β	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP	FN	FP
5	6	30	0	18	0	30	0	18	0	18	0	13	0	18	0	13	0
0.05	0.06	5	0	0	0	20	0	0	0	0	0	0	0	25	0	0	0

the model given by Equation 3. For each generated network, the connection matrix w is randomly set in the following way. Firstly, as occurs with the yeast model, we consider $N = 11$ genes, fixing one of the genes (gene 1) as the source of the network (input degree equals to zero) by making $w_{11} = w_{21} = \dots = w_{N1} = 0$. As there are 29 connections present in yeast model, 30 cells from w_{ij} , $1 \leq i, j \leq N$ are randomly chosen. For these randomly chosen cells, each one has a probability of 0.5 to be represented by activation (+1) or inhibition (-1), while all other cells remain zero. Also, considering that in yeast model, 4 out of 11 genes suffer self-degradation (approximately one third), each gene has probability $\frac{1}{3}$ to be self-degraded. If a gene i suffers self-degradation, then $w_{ii} = -0.1$.

We applied the random network generation procedure presented above to generate 10 random network topology samples. For each network topology, the

transition matrix P and the limit distribution π were computed considering both large temperature ($\alpha = 5$ and $\beta = 6$) and small temperature ($\alpha = 0.05$ and $\beta = 0.06$). Finally, these transition matrices and limit distributions were supplied as inputs to the four inference methods considered (ES-CoD, ES-UC, SFS-CoD, SFS-UC). The numbers of false negatives (FN) and false positives (FP) obtained for each method applied to each considered sample are shown in Table 1. Table 2 summarizes these results presenting the mean and standard deviation values.

Table 2. Averages and standard deviations of the results presented in Table 1

	ES-CoD		ES-UC		SFS-CoD		SFS-UC	
	FN	FP	FN	FP	FN	FP	FN	FP
$(\alpha = 5, \beta = 6)$ averages	7.8	0	4.5	0	11.7	0	4.5	0.2
$(\alpha = 5, \beta = 6)$ std. dev.	10.4	0	6.8	0	8.3	0	6.8	0.4
$(\alpha = 0.05, \beta = 0.06)$ averages	1.2	0	0	0	17.8	0	0	0
$(\alpha = 0.05, \beta = 0.06)$ std. dev.	2.0	0	0	0	4.6	0	0	0

The first important observation that can be drawn from Tables 1 and 2 is that the inference accuracy of the uncertainty coefficient for both exhaustive search and SFS is significantly better than the accuracy obtained by the application of CoD. In fact, CoD performs very poorly especially when embedded in the SFS algorithm, since in average, the percentage of recovery is around 50% (15 out of 30) of the connections. Moreover, for the sample 9 considering $\alpha = 5$ and $\beta = 6$, CoD was incapable to identify any connection even when exhaustive search was applied (i.e., CoD was zero for all possible subsets of all genes considered as targets). On the other hand, SFS performed nicely when guided by the uncertainty coefficient, having a very small number of false negatives in average, although it obtained one false positive in two cases.

These results can be explained by the fact that, in many cases, the Bayesian error does not decrease by adding features, even that such features offer some gain of information about the target behavior (i.e., the average entropy decreases). Table 3 refers to an example where the prior Bayesian error of the target Y is not improved by including the feature X ($CoD_Y(X) = 0$), while the prior entropy of Y is decreased by the information of X ($UC_Y(X) = 0.065$). Figure 1 illustrates this same example in graphics with the Bayesian error and entropy values for $P(Y = 1)$, $P(Y = 1|X = 0)$ and $P(Y = 1|X = 1)$. As $P(X = 0) = P(X = 1)$, the mean conditional entropy of Y given X becomes smaller than the prior entropy, since $|H(Y|X = 1) - H(Y)|$ is smaller than $|H(Y|X = 0) - H(Y)|$, which leads to a positive $UC_Y(X)$. On the other hand, since $|\varepsilon(Y|X = 1) - \varepsilon(Y)| = |\varepsilon(Y|X = 0) - \varepsilon(Y)|$, the Bayesian error of Y given X remains the same as the prior Bayesian error, which leads to $CoD_Y(X) = 0$.

Table 3. Example that illustrates a case where $CoD_Y(X) = 0$ and $UC_Y(X) > 0$. (a) Probability distribution of the target Y ($\varepsilon(Y) = 0.2$ and $H(Y) = 0.722$); (b) Joint probability distribution of X and Y ($\varepsilon(Y|X) = 0.2 \rightarrow CoD(Y|X) = \frac{0.2-0.2}{0.2} = 0$ and $H(Y|X) = 0.675 \rightarrow UC_Y(X) = \frac{0.722-0.675}{0.722} = 0.065$).

Fig. 1. These graphics illustrate why the mean conditional entropy of Y given X is smaller than the prior entropy of Y and the Bayesian error of Y given X is the same as the prior Bayesian error of Y for the joint probability distributions presented on Table 3.

5 Conclusion

Considering an ideal setting where all state transition probabilities of a gene regulatory network are known, experiments using stochastic restricted Boolean networks have shown that the adoption of a feature selection criterion based on conditional entropy (uncertainty coefficient) performed a significantly better inference than that obtained by the application of a Bayesian error based criterion (non-linear coefficient of determination). This happens because, in many situations, the prior error of the target feature is not improved by the knowledge of other features even that there is some information provided by such features (i.e. the prior entropy decreases). More importantly, the SFS algorithm had very nice results when guided by the uncertainty coefficient, which could be an indicative that this approach may be used to accurately infer a network containing thousands of genes in a small time interval, even when hubs are present, i.e. genes influenced by five or more genes.

However, real microarray experiments do not provide all state transition probabilities. In fact, only a few dozens of samples are available and the error estimation becomes an important issue to address. Certainly, inference of networks

from limited number of data samples could imply a qualitative change in the results presented here. In this sense, a future step of this research is to consider the same comparison in small sets of temporal gene expression signals. But, in principle, there is no reason to think that entropy-based criteria could perform worse than Bayesian error criteria in such situations.

We also plan to extend the comparison to more general stochastic Boolean networks, since the restricted Boolean networks do not allow some specific Boolean logic functions that can not be expressed by linear functions (e.g. exclusive-or and its negated version, considering logics with two predictor features).

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