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# An Optimal Boolean Approach for Computational Modeling of Gene Regulatory Networks from Temporal Gene Expression Profile

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*ABSTRACT*

Deciphering the crucial interactions among genes is one of the key issues in understanding the fundamental molecular and intracellular mechanisms of cell. Computational modeling of gene regulatory networks can be used as a powerful tool in various fields of molecular biomedicine such as identification of metabolic, regulator, and signal transduction pathways, analysis of complex genetic diseases, and drug discovery. In this paper, an optimal Boolean approach was proposed for computational modeling of gene regulatory networks from temporal gene expression profile. In this method, the optimal values of the Boolean thresholds of gene expression signals and the parameters of the interaction patterns between target and regulator genes are all designed as a mixed-integer nonlinear programming solved by Genetic Algorithm. To evaluate the performance of the proposed scheme, it has been applied to a well-known time course microarray data and gene regulatory network of *Saccharomyces cerevisiae* from the literature. The reference network has 11 genes, 9 targets, and 61 regulatory interactions, and the original transcriptional dataset includes 18 time points for each gene expression signal. In this case study, the proposed computational model contains 142 unknown parameters that are optimally determined through optimization. The results demonstrate the efficiency of the proposed approach.

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## 1. INTRODUCTION

In recent years, many researches have used the converging technologies of the industrial revolution 4.0 era to significantly affect future medicine [1, 2]. With the aid of gene expression profiling technology such as DNA microarray, it is possible to study the behavior and interactions of thousands of genes simultaneously [3, 4]. This technology is one of the most influential tools for discovering the transcriptional and translational dynamics of genes that leads to computational modeling and analysis of the interactions between genes as Gene Regulatory Networks (GRNs) [5-7]. Due to the nature of gene regulation, important mechanisms are involved in this process such as DNA, RNA, and protein interactions. Usually, the proteins that are translated from genes or produced from chemical reaction networks can play the role of transcription factors to activate or inhibit the transcription of some genes. The purpose of inferring gene regulatory networks is to decipher the interaction patterns among target and regulator genes from the spatial and temporal profiles of gene expression data. Additionally, this paradigm can lead to the identification of genes that play key roles in metabolic and signal transduction pathways. Computational modeling and analysis of GRNs demonstrate how some genes affect other genes in a complex manner. This information can be widely used in various areas of biological and medical researches such as molecular medicine, drug discovery, P4 medicine, and cell/tissue engineering [8, 9].

Different methods have been proposed in the literature for computational modeling of GRNs. Some

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of them are reviewed here. Ren and Jinde [10] described a robust analysis scheme based on Lyapunov stability theory and linear matrix inequality (LMI) for asymptotic stability of delayed GRNs with time-varying delays. Xiao et al. [11] proposed a reduced-order approach to consider the stability analysis in GRNs with discrete time delays. Zañudo et al. [12] used the notion of discrete dynamic networks to investigate how computational modeling of oncogenic signaling can help personalized treatment of cancer. Chen et al. [13] proposed a Markovian method for controlling the dynamics of GRNs. Barbuti et al. [14] reviewed various techniques used in mathematical modeling of GRNs including ordinary differential equations (ODE), Boolean networks, Petri nets, P systems, and reaction systems.

Mandon et al. [15] considered attractor-based sequential reprogramming of GRNs based on Boolean network models. Dai and Liu [16] proposed a computational approach for inferring gene-gene interactions from time-series data based on Bayesian network modeling, estimation of distribution algorithms, and depth-first search. Hajiramezanali et al. [17] presented optimal classification of cellular trajectories under regulatory model uncertainty based on partially-observed Boolean dynamical systems and noisy gene expression data. In recent years, special attention has been focused on computational modeling and analysis of GRNs based on time-course gene expression data, as reported inliterature [18-20], that is the main topic of this study.

In this paper, we propose an optimal Boolean approach for computational modeling of GRNs from temporal gene expression profile. Both fundamental steps of systems identification including Model Structure Design and Parameter Optimization are described. The proposed model structure is a general and computationally efficient model which contains four set of parameters including expression threshold, regulator weight, regulator delay, and activation limit. The parameter optimization is formulated as a mixed-integer nonlinear programming. In order to solve this optimization problem in a general manner, Genetic Algorithm (GA) is used. Furthermore, a general preprocessing method is introduced for normalization and smooth interpolation of gene expression time series. To evaluate the performance of the proposed model, it is applied to a benchmark time course microarray data and reference gene regulatory network of *Saccharomyces cerevisiae* from the literature. The results demonstrate that the proposed approach could accurately model the benchmark GRN with more simplicity and understandability.

This paper is organized as follows: In the next section, the reference gene regulatory network and the time-course transcriptional dataset of the case study of this paper are described. Then, a general preprocessing method is introduced for normalization and interpolation of gene expression time series. In section 3, an optimal Boolean approach is proposed for computational modeling of GRNs from temporal gene expression profile. The results of evaluation are demonstrated in section 4. Finally, section 5 concludes the paper.

## 2. TEMPORAL GENE EXPRESSION PROFILE

**2. 1. The Reference GRN** Gene regulation is one of the key mechanisms in cell cycle control, when proper functioning of the cell cycle is vital for the survival of an organism. Functional abnormalities in cell cycle process may lead to noteworthy alterations in the phenotypical aspects of the cell and even, programmed cell death. Yeasts, the eukaryotic single-celled microorganisms as members of the fungus kingdom, have been widely used in systems biology for studying cell cycle control especially from genomic perspective [21]. Many remarkable investigations have been performed in the literature on the cell cycle of *Saccharomyces cerevisiae* as a well-known species of yeast. Most of these researches have been focused on the gene regulatory networks and the spatial and temporal profiles of gene expression which are incorporated in the mechanisms of cell cycle control. In general, these studies on yeast microorganisms are valuable because some results can be generalized to complex organisms.

In the case study of this paper, a commonly-used reference GRN [22], which play a significant role in the cell cycle control of *Saccharomyces cere*visiae, have been considered. This reference GRN have been frequently used by the previous works in the literature [23, 24]. As shown in Figure 1, the reference network has 11 genes including *cln1*, *cln2*, *cln3*, *clb1*, *clb2*, *clb5*, *clb6*, *cdc14*, *cdc20*, *mcm1*, and *swi5*. There are 9 target

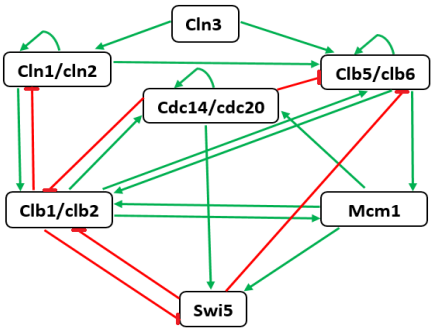



**Figure 1.** The reference gene regulatory network [22-24]

genes which are totally regulated by 61 regulatory interactions. The green arrow lines indicate which

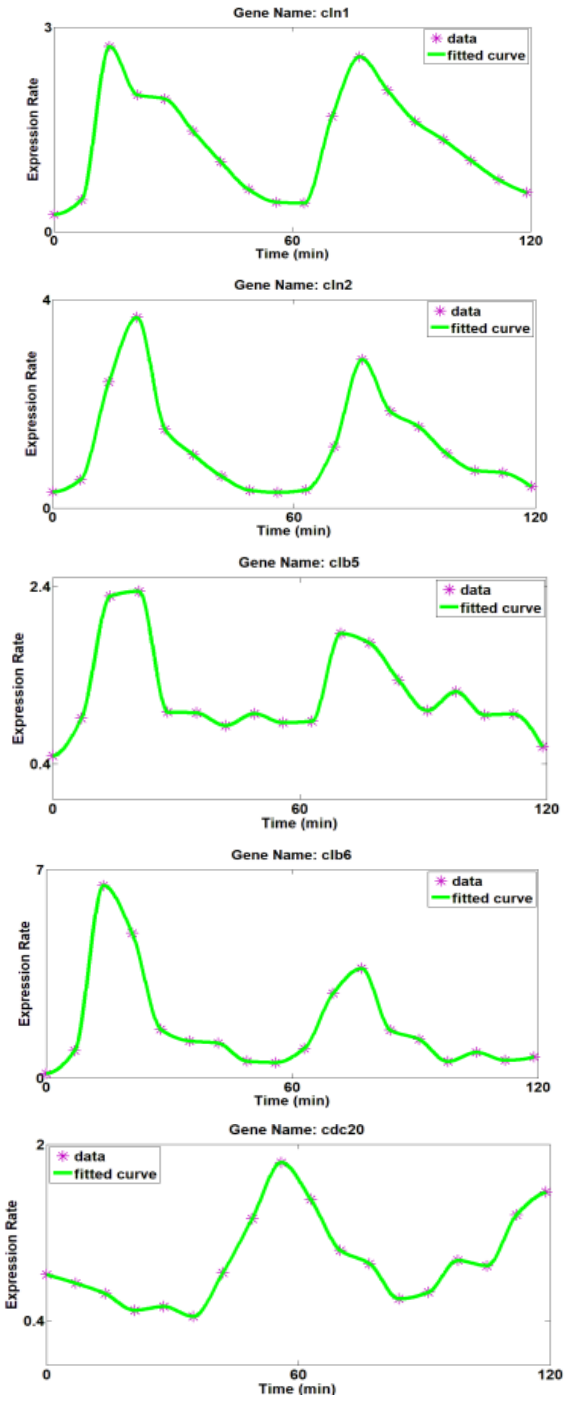
regulator genes play the role of activator and which target genes are affected by them in the form of upregulation. Similarly, the inhibitors that lead to the down-regulation of their targets are illustrated by red blocking lines. More details about this reference GRN are available in literature [22-24].

**2. 2. The Time-Course Gene Expression Data** The time-course gene expression data, measured by transcriptional profiling technologies such as DNA microarray, has been frequently exploited as training dataset for computational modeling of GRNs. In this paper, we use the well-known temporal gene expression profile of the yeast Saccharomyces cerevisiae. This dataset has been introduced by Spellman et al. [25] and it is available on Gene Expression Omnibus (GEO) with accession number of GSE22[1]. In the mentioned dataset, the expression levels of genes have been measured over 2 hours with sampling period of 7 minutes. Thus, the training dataset includes the time series with 18 time points for each gene.

**2. 3. Preprocessing Procedure** In this paper, a general preprocessing method is introduced for normalization and interpolation of gene expression time series. In order to consider the effect of down-regulation and up-regulation of genes accurately, normalization of the magnitude of gene expression levels is required. Also, in most of the transcriptional profiling procedures, the value of sampling period is large. But most of the computational models of GRN need more number of samples to increase the identification accuracy. For this reason, interpolation can be an effective approach to provide smooth approximated signals from original time course gene expression dataset. Here, we use shape-preserving piece-wise cubic Hermite interpolation technique that is an appropriate scheme from the aspects of computational efficiency and smoothness [26]. Particularly in the continuous-time models of GRN such as ODE models, in which precise approximation of the derivatives of expression signals are required, the above-mentioned interpolation procedure can be highly helpful. Figure 2 depicts the temporal gene expression profile of the case study after preprocessing.

## 3. THE PROPOSED MODELING APPROACH

**3. 1. Boolean Model Structure** A system identification problem consists of two fundamental steps: a) Model Structure Selection, and b) Parameter Optimization. In this paper, a general but computationally simple Boolean model structure is proposed for computational modeling of GRNs. Transparency and understandability of model structure are important desirable characteristics. The proposed Boolean model structure is shown in Figure 3. This model contains four set of parameters: 1) Expression Threshold, 2) Regulator Weight, 3) Regulator Delay, and 4) Activation Limit.




[1] https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE22

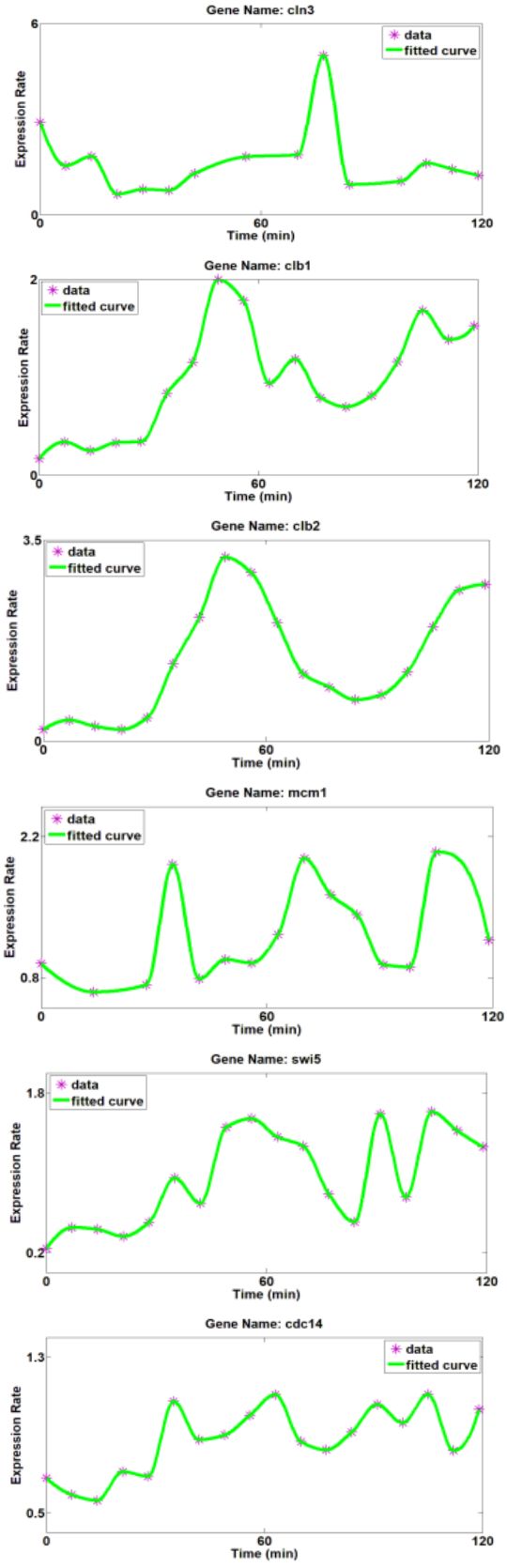



**Figure 2.** The temporal gene expression profile after preprocessing

In Boolean models of GRNs, genes are considered to be On or Off. Since the gene expression level is a real-valued variable, a threshold is required to convert this continuous signal to a binary one. As the dynamics and molecular function of genes are different, due to the generality, an independent expression threshold parameter is defined for each gene. Also, the effects of regulators on their target gene are not generally the same. To address this issue, we define independent Weight and Delay parameters for each regulator-target interaction link. Weight illustrates the intensity of regulation between a regulator and its target, and Delay represents how late this regulation is affected. Finally, in order to aggregate the regulatory effects of activators and inhibitors on a target gene, an activation limit is defined for each target.

As shown in Figure 3, for the case study of this paper, the proposed Boolean model structure has totally 142 parameters including 11 parameters for expression threshold, 61 for regulator weight, 61 for regulator delay, and 9 for activation limit. The governing equations of this model are as follows:

$$G_{cln1}(k+1) = H((A_{cln1}(k) - I_{cln1}(k) - B_{cln1}(k)) \quad (1)$$

$$A_{cln1}(k) = W_{cln1}^{cln1} * G_{cln1}\left(k - d_{cln1}^{cln1}\right) + W_{cln1}^{cln2} * G_{cln2}\left(k - d_{cln1}^{cln2}\right) + W_{cln1}^{cln3} * G_{cln3}\left(k - d_{cln1}^{cln3}\right)$$

$$I_{cln1}(k) = W_{cln1}^{clb1} * G_{clb1}\left(k - d_{cln1}^{clb1}\right) + W_{cln1}^{clb2} * G_{clb2}\left(k - d_{cln1}^{clb2}\right) \quad (2)$$

$$G_{cln2}(k+1) = H((A_{cln2}(k) - I_{cln2}(k) - B_{cln2}(k))$$

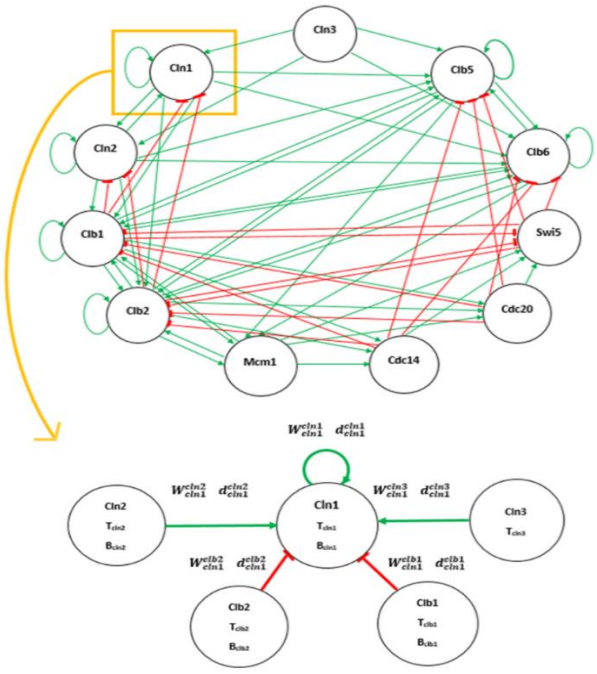



**Figure 3.** The proposed model structure

$$A_{cln2}(k) = W_{cln2}^{cln2} * G_{cln2}\left(k - d_{cln2}^{cln2}\right)) + W_{cln2}^{cln1} * G_{cln1}\left(k - d_{cln2}^{cln1}\right) + W_{cln2}^{cln3} * G_{cln3}\left(k - d_{cln2}^{cln3}\right)$$

$$I_{cln2}(k) = W_{cln2}^{clb1} * G_{clb1}\left(k - d_{cln2}^{clb1}\right) + W_{cln2}^{clb2} * G_{clb2}\left(k - d_{cln2}^{clb2}\right) \quad (3)$$

$$G_{clb5}(k+1) = H((A_{clb5}(k) - I_{clb5}(k) - B_{clb5}(k))$$

$$A_{clb5}(k) = W_{clb5}^{clb5} * G_{clb5}\left(k - d_{clb5}^{clb5}\right) + W_{cln5}^{cln1} * G_{cln1}\left(k - d_{clb5}^{cln1}\right) + W_{clb5}^{cln2} * G_{cln2}\left(k - d_{clb5}^{cln2}\right) + W_{clb5}^{cln3} * G_{cln3}\left(k - d_{clb5}^{cln3}\right) + W_{clb5}^{clb1} * G_{clb1}\left(k - d_{clb5}^{clb1}\right) + W_{clb5}^{clb2} * G_{clb2}\left(k - d_{clb5}^{clb2}\right) + W_{clb5}^{clb6} * G_{clb6}\left(k - d_{clb5}^{clb6}\right) \quad (4)$$

$$I_{clb5}(k) = W_{clb5}^{swi5} * G_{swi5}\left(k - d_{clb5}^{swi5}\right) + W_{clb5}^{cdc20} * G_{cdc20}\left(k - d_{clb5}^{cdc20}\right) + W_{clb5}^{cdc14} * G_{cdc14}\left(k - d_{clb5}^{cdc14}\right)$$

$$G_{clb6}(k+1) = H((A_{clb6}(k) - I_{clb6}(k) - B_{clb6}(k))$$

$$A_{clb6}(k) = (W_{clb6}^{clb6} * G_{clb6}\left(k - d_{clb6}^{clb6}\right) + W_{cln6}^{cln1} * G_{cln1}\left(k - d_{clb6}^{cln1}\right) + W_{clb6}^{cln2} * G_{cln2}\left(k - d_{clb6}^{cln2}\right) + W_{clb6}^{cln3} * G_{cln3}\left(k - d_{clb6}^{cln3}\right) + W_{clb6}^{clb1} * G_{clb1}\left(k - d_{clb6}^{clb1}\right) + W_{clb6}^{clb2} * G_{clb6}\left(k - d_{clb6}^{clb2}\right) + W_{clb6}^{clb5} * G_{clb5}\left(k - d_{clb6}^{clb5}\right))$$

$$I_{clb6}(k) = \left(W_{clb6}^{swi5} * G_{swi5}\left(k - d_{clb6}^{swi5}\right) + W_{clb6}^{cdc20} * G_{cdc20}\left(k - d_{clb6}^{cdc20}\right) + W_{clb6}^{cdc14} * G_{cdc14}\left(k - d_{clb6}^{cdc14}\right)\right) \quad (5)$$

$$G_{cdc20}(k+1) = H((A_{cdc20}(k) - I_{cdc20}(k) - B_{cdc20}(k))$$

$$A_{cdc20}(k) = (W_{cdc20}^{clb1} * G_{clb1}\left(k - d_{cdc20}^{clb1}\right) + W_{cdc20}^{clb2} * G_{clb2}\left(k - d_{cdc20}^{clb2}\right) + W_{cdc20}^{mcm1} * G_{mcm1}\left(k - d_{cdc20}^{mcm1}\right)) \quad (6)$$

$$I_{cdc20}(k) = 0$$

$$G_{clb1}(k+1) = H((A_{clb1}(k) - I_{clb1}(k) - B_{clb1}(k))$$

$$A_{clb1}(k) = (W_{clb1}^{clb1} * G_{clb1}\left(k - d_{clb1}^{clb1}\right) + W_{clb1}^{clb2} * G_{clb2}\left(k - d_{clb1}^{clb2}\right) + W_{clb1}^{clb5} * G_{clb5}\left(k - d_{clb1}^{clb5}\right) + W_{clb1}^{clb6} * G_{clb6}\left(k - d_{clb1}^{clb6}\right) + W_{clb1}^{cln1} * G_{cln1}\left(k - d_{clb1}^{cln1}\right) + W_{clb1}^{cln2} * G_{cln2}\left(k - d_{clb1}^{cln2}\right) + W_{clb1}^{mcm1} * G_{mcm1}\left(k - d_{clb1}^{mcm1}\right)) \quad (7)$$

$$I_{clb1}(k) = W_{clb1}^{swi5} * G_{swi5}\left(k - d_{clb1}^{swi5}\right) + W_{clb1}^{cdc20} * G_{cdc20}\left(k - d_{clb1}^{cdc20}\right) + W_{clb1}^{cdc14} * G_{cdc14}\left(k - d_{clb1}^{cdc14}\right)$$

$$G_{clb2}(k+1) = H((A_{clb2}(k) - I_{clb2}(k) - B_{clb2}(k))$$

$$A_{clb2}(k) = (W_{clb2}^{clb2} * G_{clb2}\left(k - d_{clb2}^{clb2}\right) + W_{clb2}^{clb1} * G_{clb1}\left(k - d_{clb2}^{clb1}\right) + W_{clb2}^{clb5} * G_{clb5}\left(k - d_{clb2}^{clb5}\right) + W_{clb2}^{clb6} * G_{clb6}\left(k - d_{clb2}^{clb6}\right) + W_{clb2}^{cln1} * G_{cln1}\left(k - d_{clb2}^{cln1}\right) + W_{clb2}^{cln2} * G_{cln2}\left(k - d_{clb2}^{cln2}\right) + W_{clb2}^{mcm1} * G_{mcm1}\left(k - d_{clb2}^{mcm1}\right)) \quad (8)$$

$$I_{clb2}(k) = W_{clb2}^{swi5} * G_{swi5}\left(k - d_{clb2}^{swi5}\right) + W_{clb2}^{cdc20} * G_{cdc20}\left(k - d_{clb2}^{cdc20}\right) + W_{clb2}^{cdc14} * G_{cdc14}\left(k - d_{clb2}^{cdc14}\right)$$

$$G_{mcm1}(k+1) = H((A_{mcm1}(k) - I_{mcm1}(k) - B_{mcm1}(k))$$

$$A_{mcm1}(k) = (W_{mcm1}^{clb1} * G_{clb1}\left(k - d_{mcm1}^{clb1}\right) + W_{mcm1}^{clb2} * G_{clb2}\left(k - d_{mcm1}^{clb2}\right) + W_{mcm1}^{clb5} * G_{clb5}\left(k - d_{mcm1}^{clb5}\right) + W_{mcm1}^{clb6} * G_{clb6}\left(k - d_{mcm1}^{clb6}\right)) \quad (9)$$

$$I_{mcm1}(k) = 0$$

$$G_{swi5}(k+1) = H((A_{siw5}(k) - I_{siw5}(k) - B_{siw5}(k))$$

$$A_{siw5}(k) = (W_{swi5}^{cdc14} * G_{cdc14}\left(k - d_{siw5}^{cdc14}\right) + W_{swi5}^{mcm1} * G_{mcm1}\left(k - d_{siw5}^{mcm1}\right)) \quad (10)$$

$$I_{siw5}(k) = \left(W_{swi5}^{clb1} * G_{clb1}\left(k - d_{siw5}^{clb1}\right) + W_{swi5}^{clb2} * G_{clb2}\left(k - d_{siw5}^{clb2}\right)\right)$$

where $G_X$ is the normalized expression level of gene $X$, $A_T$ is the activation term which leads to the upregulation of target gene $T$, $I_T$ is the inhibition term which leads to the downregulation of target gene $T$, $B_T$ is the activation limit for target gene $T$, $H$ is the Hard-limit function, $W_T^R$ and $d_T^R$ are respectively the weight and delay of the regulatory effect of regulator $R$ on target $T$, and $k$ is the number of timepoint in the interpolated temporal profile.

**3. 2. Parameter Optimization by GA** In order to find the optimal values of the unknown parameters of the proposed Boolean model structure of the previous section, the time-course gene expression data described in section 2 is used. The parameters of Expression Threshold, Regulator Weight, and Activation Limit are real-valued, but the parameters of Regulator Delay are integer. According to this point, and with respect to the nonlinearity available in model equations and error metric, the parameter optimization problem is a mixed-integer nonlinear programming. Solving constrained nonlinear optimization problems, especially with mixed-integer decision variables, is generally difficult and conventional optimization methods may not solve these problems effectively, and consequently the exact optimal solutions cannot be found easily. Therefore, as an alternative, various metaheuristic algorithms have been proposed in the literature to efficiently find the near-optimal solutions for complex optimization problems [27-29].

One of the most powerful and general-purpose metaheuristic algorithms is GA that is recognized as derivative-free population-based global optimizer. Different versions of GA have been proposed in the literature and it has been combined with other artificial intelligence methods to improve its computational efficiency, accuracy, and convergence speed for diverse

types of optimization problems including constrained, multi-objective, nonlinear, nonconvex, mixed-integer, and largescale problems [30-32]. More importantly, GA has been widely used in different domains of applications such as food science [33], control engineering [34], medicine [35], nanotechnology [36], machine learning [37], and civil engineering [39, 39]. As shown in Figure 4, GA is applied to solve the mixed-integer nonlinear programming of this study.

## 4. RESULTS

In this section, GA is used for parameter optimization of the proposed Boolean model structure of section 3.1. As the training dataset, the preprocessing procedure introduced in section 3.3 was applied to the benchmark temporal gene expression profile of section 3.2, and the interpolated time series were sampled at a period of 5 minutes. We used the genetic algorithm solver of Global Optimization Toolbox in MATLAB. Figure 5 represents the relative values of Expression Threshold for each gene. As displayed in this figure, the expression threshold has a distinguishing value for each gene. Figure 6 demonstrates the output of the proposed optimal Boolean model in comparison with the temporal gene expression profile in a Boolean manner. The blue dots are the actual values and the red circles are the values identified by the proposed method. The identification error is 17.59% in terms of mean absolute error.

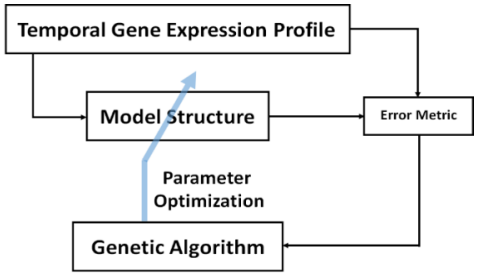



**Figure 4.** Parameter optimization by Genetic Algorithm

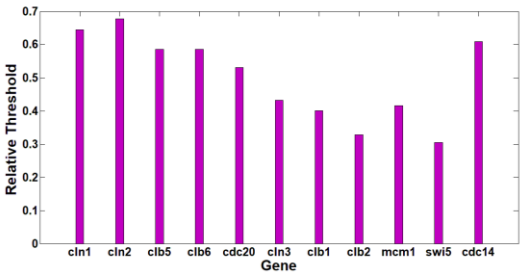
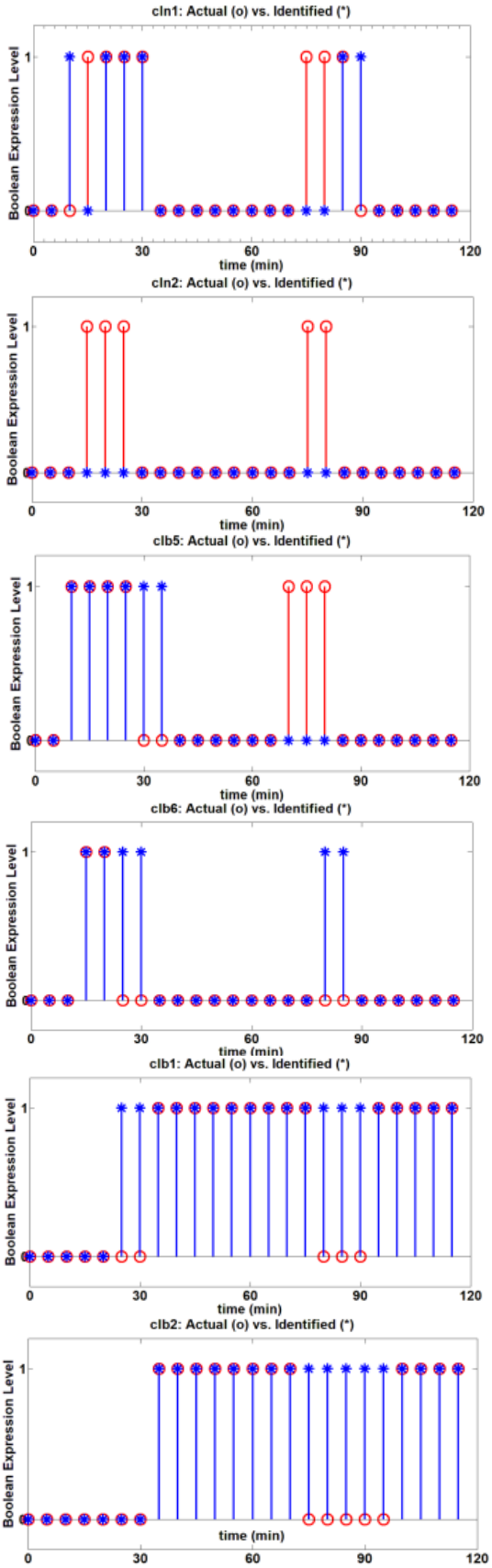



**Figure 5.** The relative values of Expression Threshold for each gene



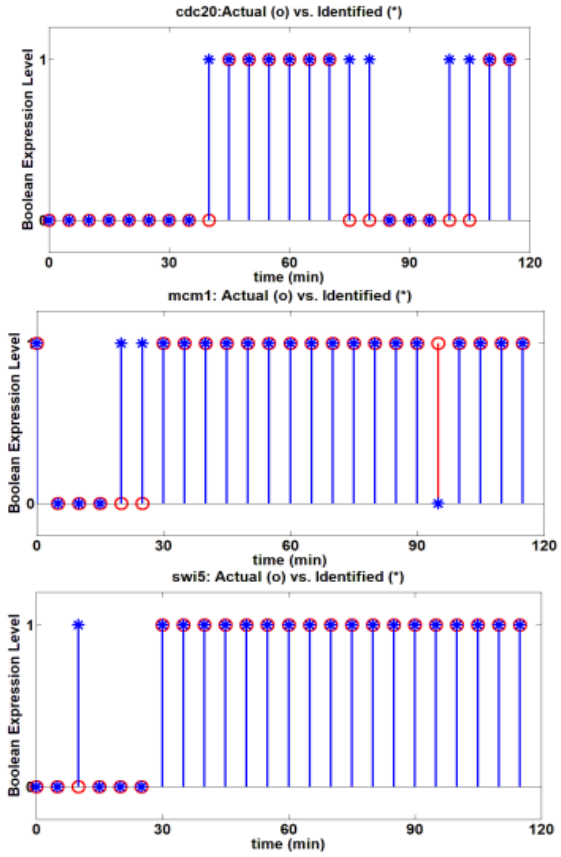



**Figure 6.** The output of the proposed model (identified) vs. the temporal gene expression profile (actual)

## 5. CONCLUSION

This paper proposed an optimal Boolean approach for computational modeling of gene regulatory networks from the temporal transcriptional data. The model structure is a flexible and computationally efficient model which contains four sets of parameters including expression threshold, regulator weight, regulator delay, and activation limit. The parameter optimization was formulated as a mixed-integer nonlinear programming and solved by genetic algorithm. Also, a general preprocessing method was introduced for normalization and interpolation of gene expression time series. To evaluate the performance of the proposed approach, it has been applied to a well-known time-course microarray data and reference gene regulatory network of *Saccharomyces cerevisiae* from the literature. The reference network has 11 genes, 9 targets, and 61 regulatory interactions, and the original transcriptional dataset includes 18 timepoints for each gene expression signal. The proposed model contains 142 unknown parameters. The results demonstrated that the proposed model could successfully identify the gene regulatory network with the identification error of 17.59% in terms of mean absolute error.

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## Persian Abstract

**چکیده**

رمزگشایی از فعل و انفعالات حیاتی بین ژن ها یکی از موضوعات اصلی در درک مکانیسم های بنیادی مولکولی و درون سلول است. مدل سازی محاسباتی شبکه های تنظیم کننده ژن می تواند به عنوان ابزاری قدرتمند در زمینه های مختلف زیست پزشکی مولکولی مانند شناسایی مسیرهای متابولیکی، تنظیم کننده و سیگنالینگ، همچنین تجزیه و تحلیل بیماری های پیچیده و کشف دارو استفاده شود. در این مقاله، یک روش بولین بهینه برای مدل سازی محاسباتی شبکه های تنظیم کننده ژن مبتنی بر پروفایل زمانی داده های بیان ژن پیشنهاد شده است. در این روش، مقادیر بهینه آستانه بولین سیگنال های بیان ژن و پارامترهای الگوی برهم کنش بین ژن های هدف و ژن های تنظیم کننده همگی در قالب یک برنامه ریزی غیرخطی مختلط طراحی شده که توسط الگوریتم ژنتیک حل می‌شود. جهت ارزیابی روش پیشنهادی، از آن برای مدلسازی شبکه تنظیم کننده ژن *ساکارومایسس سرویزیه* مبتنی بر پروفایل زمانی داده های بیان ژن استفاده شده است. شبکه مرجع دارای ۱۱ ژن است که ۹ ژن هدف و ٦١ برهم کنش تنظیمی را شامل می شود. در دیتاست اصلی مربوط به پروفایل زمانی داده های ترانسکریپتومیکس، هر سیگنال بیان ژن شامل ۱۸ نمونه زمانی است. در این مطالعه موردی، مدل محاسباتی پیشنهادی شامل ١٤٢ پارامتر ناشناخته است که از طریق بهینه سازی توسط الگوریتم ژنتیک تعیین می شوند. نتایج بدست آمده کارایی روش پیشنهادی را نشان می دهند.