



Inferring causal networks using fuzzy cognitive maps and evolutionary algorithms with application to gene regulatory network reconstruction

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ARTICLE INFO

Article history:

Received 4 September 2014

Received in revised form 2 August 2015

Accepted 14 August 2015

Available online 7 September 2015

Keywords:

Evolutionary algorithms
Fuzzy cognitive map
Gene regulatory networks
Learning algorithm
Optimization

ABSTRACT

Fuzzy cognitive maps have been widely used as abstract models for complex networks. Traditional ways to construct fuzzy cognitive maps rely on domain knowledge. In this paper, we propose to use fuzzy cognitive map learning algorithms to discover domain knowledge in the form of causal networks from data. More specifically, we propose to infer gene regulatory networks from gene expression data. Furthermore, a new efficient fuzzy cognitive map learning algorithm based on a decomposed genetic algorithm is developed to learn large scale networks. In the proposed algorithm, the simulation error is used as the objective function, while the model error is expected to be minimized. Experiments are performed to explore the feasibility of this approach. The high accuracy of the generated models and the approximate correlation between simulation errors and model errors suggest that it is possible to discover causal networks using fuzzy cognitive map learning. We also compared the proposed algorithm with ant colony optimization, differential evolution, and particle swarm optimization in a decomposed framework. Comparison results reveal the advantage of the decomposed genetic algorithm on datasets with small data volumes, large network scales, or the presence of noise.

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1. Introduction

Fuzzy cognitive map (FCM) is a graph model that visualizes expert knowledge as a weighted directed graph [1]. The nodes in FCMs represent the concepts to be modeled, and the signed weights between the nodes represent the strength of causal relations. Traditionally, the initial weights are assigned by domain experts. In addition, Hebbian-based learning algorithms [2–4] can be used to resolve conflicts among experts and to improve the accuracy of the weights. The resulting FCM model can be used to study the properties of the complex system under investigation.

There are several advantages in applying FCMs to model complex systems. Because FCMs do not have hidden nodes, the dynamics of the system can be interpreted easily in terms of interactions among a set of well-defined, real-world concepts. Domain experts can also use linguistic terms to define the weights, and the simulation results can thus be easily interpreted in linguistic terms. Furthermore, FCMs can also generate rich dynamics although the models are simple [5]. Due to these advantages, FCMs have been applied to study a wide variety of complex systems, such as, engineering control systems [6–8], on-line design of fuzzy controllers

[9–11], situation-aware computing [12], medical decision support systems [13–15], educations [16], and ecosystems [17]. FCMs have also been used together with other techniques to model complex systems. Examples include cellular automata [18], gray system theory [19], and petri nets [20].

In spite of the wide application areas of FCMs, to the best of our knowledge, there is no report on applying FCMs to the causal inference problems. Different from the other applications of FCMs where domain knowledge is applied to construct FCMs, the application of FCMs to causal inference may help discover new domain knowledge.

Causal inference is an important problem which mainly focuses on discovering plausible causal relations between the concepts or nodes. An example of causal inference problem is the reverse engineering of gene regulatory networks (GRNs). GRNs consist of genes and their interaction relations. The expression level of a gene may cause an increase (activation) or decrease (repression) in the expression level of another gene. These causal relations among the genes are critical to understanding the functions of the cells [21]. However, many of these relations are unknown to domain experts and therefore causal inference algorithms are needed to discover these relations.

Although many methods have been developed to infer GRNs from gene expression data [22], we believe FCMs could be used to better represent and discover the relations in GRNs. The most widely used method in the literature include Boolean networks [23,24], Bayesian networks [25], dynamic Bayesian networks [26], ordinary differential equations [27,28], and correlation and mutual information based methods [29,30]. These methods represent the gene expression levels using either Boolean values or scaled real values. Applying FCMs to GRN inference problems

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Table 1
Size of FCMs (maximum number of nodes) in previous studies.

Reference	Year	Algorithm	Size
Koulouriotis et al. [42]	2001	Evolutionary strategies	6
Parsopoulos et al. [43]	2003	PSO	5
Papageorgiou and Groumos [44]	2005	Hybrid DE and nonlinear HL	8
Papageorgiou et al. [45]	2006	Active HL/nonlinear HL	5
Ghazanfari et al. [46]	2007	Hybrid RCGA and SA	15
Stach et al. [47]	2007	Parallel RCGA	80
Stach et al. [48]	2008	Data-driven nonlinear HL	20
Alizadeh and Ghazanfari [49]	2009	Chaotic SA	14
Petalas et al. [37]	2009	Memetic PSO	18
Stach et al. [32]	2010	Divide and conquer RCGA	40
Baykasoglu et al. [50]	2011	Extended great deluge	6
Zhang et al. [51]	2011	Gradient residual algorithm	7
Madeiro and Zuben [52]	2012	RCGA with gradient search	38
Stach et al. [34]	2012	Sparse RCGA	40
Chen et al. [35]	2012	ACO	40
Chen et al. [53]	2012	Decomposed ACOR	100
Shen and Huang [54]	2013	Extreme learning machine	6
Yesil et al. [55]	2013	Artificial bee colony	13
Gregor and Groumos [56]	2013	Gradient-based search	20
Kannappan and Papageorgiou [57]	2013	Artificial immune systems	26
Napoles and Papageorgiou [58]	2014	Hybrid PSO and ACO	25
This paper	–	Decomposed RCGA with tournament selection	300

ACO, ant colony optimization; ACOR, ACO for real parameters; DE, differential evolution; HL, Hebbian learning; PSO, particle swarm optimization; RCGA, real-coded genetic algorithm; SA, simulated annealing.

could provide a good balance between the Boolean and real value representation methods and could potentially outperform the existing methods.

In this paper, we propose to apply FCM learning algorithms to construct GRNs from data. Although there are existing FCM learning algorithms that could be applied to construct FCMs from data, there are several concerns need to be addressed, including whether the existing FCM learning framework could be applied to causal inference problem, which algorithm performs the best for this particular problem, and how to learn FCMs with a large number of nodes. These three concerns are further discussed in the following.

- (1) *The applicability of FCM learning algorithms to the reverse engineering of complex causal networks.* Research advances in FCM learning algorithms provide the opportunity to discover knowledge from historical data; however, to the best of our knowledge, there is no report on the reverse engineering of causal networks using FCMs. Most of the studies apply data-driven FCM learning algorithms to problems focused on minimizing the difference between an output sequence and historical data, *i.e.*, the simulation error [31–33]. However, reverse engineering of causal networks requires an accurate estimation of the weights, *i.e.*, minimizing the model error, which is not directly related to simulation error. Usually, there are many different FCMs with the same or very similar simulation results. The implications of this for the discovery of causal networks are not well-understood. Several studies have assessed the accuracy of weights in the learned FCMs [34,35]. However, the accuracy of the FCMs is relatively low and it is unknown if there is a significant correlation between the accuracy of simulation result and the accuracy of the structures and weights of the FCMs. The *first aim* of this paper is to evaluate the FCM learning algorithms using structure-based performance measures and determine if simulation accuracy can be used as a reliable objective function in reverse engineering applications.
- (2) *The choice of optimization algorithms.* Although a large number of meta-heuristic FCM learning algorithms exist and several reviews [33,36] can be found in the literature, there are very few comprehensive comparisons [37]. Furthermore, the best algorithm for one application area may not be the best for another, including the application and objective function used in this paper. The *second aim* of this paper is to compare the performance of several widely used algorithms, including an ant colony optimization algorithm for real parameters (ACOR) [38], a differential evolution (DE) algorithm [39], a particle swarm optimization (PSO) algorithm [40,41], and a variant of real-coded genetic algorithm (RCGA) proposed in this paper.
- (3) *The applicability of the meta-heuristic algorithms to large-scale FCM learning problems.* It is difficult to learn large scale FCMs because the search space grows exponentially with the number of nodes [35]. Most learning algorithms have been applied to FCMs with a small number of nodes as summarized in Table 1. Only a few studies have tried to learn large scale FCMs. For example, Stach et al. proposed four versions of RCGA to learn FCMs with 40 nodes [32,34,59] and 80 nodes [47], respectively. Chen et al. [53] applied an ant colony optimization algorithm to learn FCMs with 100 nodes, but the accuracy was relatively low. For real-world problems, such as gene regulatory network (GRN) inference, there could be more than 100 nodes. The *third aim* of this paper is thus to propose a new FCM learning algorithm based on RCGA with tournament selection [60] and

a decomposed problem formulation [53]. The proposed algorithm is applied to large scale FCMs with up to 300 nodes.

The rest of the paper is organized as follows. Section 2 introduces the necessary background on FCMs, data-driven FCM learning algorithms and the GRN inference problem. Section 3 provides a description of the proposed FCM learning algorithm based on RCGA. Section 4 presents the experimental design. Section 5 presents the results and Section 6 summarizes the main contributions of this paper.

2. Background

2.1. Fuzzy cognitive maps

Fuzzy cognitive maps (FCMs) were proposed by Kosko as a generalization of cognitive maps [1]. An FCM is a graph with N_N nodes. Every node represents a concept in the system under investigation. Values ranging [0,1] are assigned to the nodes to represent the status (or activation degrees in FCM terminology) of the nodes. The value of node i is denoted as C_i ($i = 1, 2, \dots, N_N$). The nodes are connected with directed and weighted edges. The directions of the edges represent the causal effect of nodes on each other. Take the FCM shown in Fig. 1 as an example. There is an edge from node 1 to node 2, which means that any change in the value of node 1 will cause a change in the value of node 2. The weight of the edge from node i to node j is denoted as $w_{ij} \in [-1,1]$. A positive w_{ij} represents an excitatory relation from node i to node j , *i.e.*, an increase (decrease) in C_i will cause an increase (decrease) in C_j , while a negative w_{ij} represents an inhibitory relation, *i.e.*, an increase (decrease) in C_i will cause a decrease (increase) in C_j . The weight w_{ij} is 0 if there is no causal relation from node i to node j .

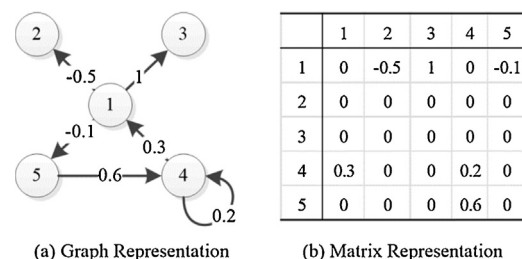


Fig. 1. An example of a FCM and its equivalent weight matrix.

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