

An approach for reduction of false predictions in reverse engineering of gene regulatory networks



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ABSTRACT

A gene regulatory network discloses the regulatory interactions amongst genes, at a particular condition of the human body. The accurate reconstruction of such networks from time-series genetic expression data using computational tools offers a stiff challenge for contemporary computer scientists. This is crucial to facilitate the understanding of the proper functioning of a living organism. Unfortunately, the computational methods produce many false predictions along with the correct predictions, which is unwanted. Investigations in the domain focus on the identification of as many correct regulations as possible in the reverse engineering of gene regulatory networks to make it more reliable and biologically relevant. One way to achieve this is to reduce the number of incorrect predictions in the reconstructed networks. In the present investigation, we have proposed a novel scheme to decrease the number of false predictions by suitably combining several metaheuristic techniques. We have implemented the same using a *dataset ensemble* approach (i.e. combining multiple datasets) also. We have employed the proposed methodology on real-world experimental datasets of the SOS DNA Repair network of *Escherichia coli* and the IMRA network of *Saccharomyces cerevisiae*. Subsequently, we have experimented upon somewhat larger, *in silico* networks, namely, DREAM3 and DREAM4 Challenge networks, and 15-gene and 20-gene networks extracted from the *GeneNetWeaver* database. To study the effect of multiple datasets on the quality of the inferred networks, we have used four datasets in each experiment. The obtained results are encouraging enough as the proposed methodology can reduce the number of false predictions significantly, without using any supplementary prior biological information for larger gene regulatory networks. It is also observed that if a small amount of prior biological information is incorporated here, the results improve further w.r.t. the prediction of true positives.

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1. Introduction

Genes form the functional circuitry of all living organisms. Every biochemical reaction inside a cell occurs as a result of their complex, synergistic action, initiated due to the demands of the living body. These are controlled and guided by interactions amongst a group of inter-regulated genes. This forms a Gene Regulatory Network (GRN). Computationally, GRNs are represented with the help of directed graphs where nodes specify the genes and the regulatory interactions among them (e.g., activation or inhibition) are represented by edges (McLachlan et al., 2005). With the evolution of genetic research, a significant amount of high-quality temporal gene expression data has been generated and made avail-

able in the public domain in the form of time-series gene expression datasets (Bar-Joseph, 2004). The analysis of this data is critical for the understanding of primary cellular activities, characterising genetic functions, the diagnosis of diseases, and assessing drug effects. Consequently, this provides motivation for the worldwide research fraternity to investigate and develop computational tools for the biologically accurate analysis and interpretation of this data.

The present research endeavour is concerned with the development of a new computational tool for reconstruction of more biologically relevant GRNs from temporal gene expression profiles. Obviously, the time-series dataset has an underlying dynamical information regarding the network configuration. The structure of a GRN represents the complex controlling interactions between genes that involve DNA, RNA, protein, and other molecules. Therefore, any misinterpretation of these relationships will lead to misinformation about the system. Interactions may be of two types:

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activation and inhibition. A gene G_1 is said to be regulated by another gene G_2 , if the transcription factors programmed by G_2 are involved in regulating the expression of G_1 . If the level of expression of G_1 increases, the nature of control is termed as activation, while, if the level of expression decreases, the nature of control is termed as inhibition. Time-series microarray datasets comprise of the expression values of thousands of interacting genes but, unfortunately, they are usually contaminated with a considerable amount of experimental noise. Additionally, for real-world large-scale GRNs, the number of genes is far greater than the number of experimental observation points. This causes difficulties in the exactly correct prediction of GRNs.

Here, we have proposed a novel scheme for the reconstruction of GRNs where the number of false predictions is drastically reduced. The proposed scheme is based on the amalgamation of results obtained from several swarm intelligence based algorithms such as (i) particle swarm optimisation (PSO) algorithm (Eberhart and Kennedy, 1995); (ii) a bat algorithm (BA) (Yang, 2010) inspired version of PSO, BAPSO; (iii) a grey wolf optimisation (GWO) (Mirjalili et al., 2014) inspired version of PSO, GWPSO; and (iv) artificial bee colony (ABC) (Karaboga and Basturk, 2007) optimisation with recurrent neural network (RNN). We have implemented this RNN (Vohradsky, 2001) formalism for modelling the dynamics of the expression data. The swarm intelligence algorithms have been used to train the RNN model parameters to reproduce the original network dynamics accurately. Biological knowledge has been used to reduce the search space of network architectures, and the fundamental theory of combination has been implemented to increase the biological plausibility of the candidate solutions.

We have implemented the proposed approach to reconstruct the GRNs from six groups of datasets:

- (i) *in vivo* datasets of the IMRA network of *Saccharomyces cerevisiae* (Cantone et al., 2009),
- (ii) *in vivo* datasets of the SOS DNA repair network of *Escherichia coli* (Ronen et al., 2002),
- (iii) 10-gene DREAM3 Challenge network (Marbach et al., 2009b; 2010; Prill et al., 2010) datasets,
- (iv) 10-gene DREAM4 Challenge network (Marbach et al., 2009a) datasets,
- (v) *in silico* datasets of a 15-gene network, and
- (vi) *in silico* datasets of a 20-gene network.

The last two have been extracted from the GeneNetWeaver (GNW) (Schaffter et al., 2011) database. The motivation for using (i) and (ii) is to validate our proposed methodology against benchmark real-world GRNs. Also, we have chosen (iii) and (iv) to gauge the performance of our proposed methodology in the case of *in silico* benchmarks. We have experimented upon the last two datasets to observe the performance of our method in larger GRNs, regarding the reduction in the number of FPs. Furthermore, both (i) and (ii) contain multiple datasets. Hence, we have generated multiple datasets for the *in silico* networks (i.e. (iii)–(vi)) as well, to maintain parity of the observed results. This helps us to understand the effect of combining multiple datasets on the quality of inferred GRNs. This *dataset ensemble* approach provides interesting insight regarding the proposed methodology and provides us with the opportunity to compare this with other approaches w.r.t. to performance and efficiency which follows.

Nevertheless, the obtained results suggest that the proposed method is indeed able to reduce the number of false predictions, thus, increasing the *specificity* and *accuracy* of the inferred GRNs. Though this scheme cannot improve the number of correct predictions, it can decrease the number of incorrect regulations significantly. However, if we have a small amount of prior biological knowledge regarding the networks, the results of the proposed

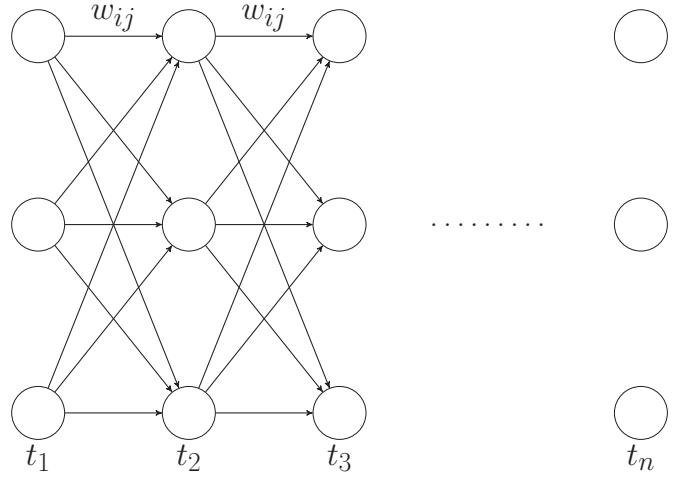


Fig. 1. A simple RNN model.

technique show further improvement in the quality of the predicted network structures w.r.t. TPs.

The rest of this paper has been organised as follows. The scientific background of the relevant topics has been presented in Section 2. The proposed methodology has been explained in detail in Section 3. Experimental results and related discussions have been presented in Section 4. The paper concludes with Section 5.

2. Preliminaries and background

2.1. Recurrent neural network (RNN)

The underlying dynamics of temporal gene expression data can be accurately captured by the RNN formalism (Vohradsky, 2001) as shown in Fig. 1. Each node denotes a gene, and an edge characterises a regulatory interaction between two genes. Each layer of the RNN defines the expression level of the genes at a specified time t_i . The expression level of a specific gene at any time-point $t_{i+1} = t_i + \Delta t$ can be obtained from the expression levels of all genes at the preceding time-point t_i , and the weights of their corresponding connecting edges w_{ij} denote the nature and strength of regulation. Mathematically, the RNN formalism that has been adopted here for modelling GRNs is as given by Vohradsky (2001):

$$x_i(t + \Delta t) = \frac{\Delta t}{\tau_i \left[1 + \exp \left(- \sum_{j=1}^N [w_{ij} x_j + \beta_i] \right) \right]} - \left(1 - \frac{\Delta t}{\tau_i} \right) x_i(t), \quad (1)$$

where $x_i(t)$ is the expression level of gene i at time-point t , and $x_i(t + \Delta t)$ is the expression level at time $t + \Delta t$. Here, β_i denotes an external input, and τ_i is a constant for each gene. The objective of the RNN formalism implemented here is to reproduce the given temporal gene expression profiles accurately by suitably training the model parameters. For training these parameters, we require the help of a metaheuristic technique. Here, we have applied PSO, BAPSO, GWPSO, and ABC. Every optimisation problem requires a fitness or objective function depending on the problem in hand. In the present context, mean square error (MSE) can be regarded as an appropriate fitness function and has been defined as follows:

$$MSE = \frac{1}{NT} \sum_1^N \sum_1^T (x_i(t) - \tilde{x}_i(t))^2, \quad (2)$$

where N is the total number of genes (nodes) in the network, T is the number of time-points, $x_i(t)$ is the original expression data and $\bar{x}_i(t)$ is the simulated data at any point of time t .

2.2. Particle swarm optimisation (PSO)

PSO is one of the simplest, robust, efficient, and easy-to-code swarm intelligence algorithms (Eberhart and Kennedy, 1995). PSO is population based and proven to return improved quality solutions compared to genetic algorithm (GA). This has been observed in a broad range of optimisation challenges with the additional benefit of having a quicker exploration rate. PSO is based on a swarm of particles that are randomly scattered in the search space. The aim of each particle is to achieve the fittest solution in the search space through social interactions with the other particles in the swarm. PSO can be defined completely by the following:

$$v'_i = w \cdot v + r_1 c_1 \cdot (p_i^b - p_i) + r_2 c_2 \cdot (g^b - p_i), \quad (3)$$

$$p'_i = p_i + v'_i, \quad (4)$$

where v'_i is the velocity of the i th particle in the next generation, v_i is the velocity in the current generation, p'_i is the position of the i th particle in the next generation, and p_i is the position in the current generation. Also, p_i^b indicates the best solution achieved by the i th particle thus far, and g^b denotes the best solution reached by the entire swarm thus far. Each particle in a swarm can be characterised completely by p , v , and p^b .

The term w is the inertia weight parameter that manages the delicate balance between the two processes of exploration and exploitation in the search space; r_1 and r_2 are random numbers uniformly drawn from $[0, 1]$ and $c_1 = c_2 = 2$. The terms $r_1 c_1$ and $r_2 c_2$ govern the influence of the best solutions achieved by a particle and the swarm, respectively, on the velocity of a particle. We have implemented a linearly decreasing scheme for w ranging from $w_{min} = 0.40$ to $w_{max} = 0.90$.

2.3. Bat algorithm inspired particle swarm optimisation (BAPSO)

Yang (2010) introduced BA, one of the recent nature-inspired metaheuristic based on the echolocation behaviour of bats. Bats transmit loud and high-pitch sounds continuously and listen to the echo from the neighbouring objects. A bat can, thus, figure out the direction and distance of any object from the received waves. In BA, the virtual bats are presumed to fly randomly, and in each generation, some of the bats are randomly selected to perform local search, i.e. exploitation. We have incorporated this quality of the virtual bats of BA into the particles in PSO, by replacing the inertia weight parameter w with r here that is a random number uniformly distributed in $[0, 1]$. Thus, in each generation of BAPSO, some of the particles will perform global search (exploration) and the remaining particles will perform local search (exploitation). Additionally, the virtual bats in BA are initially at rest, i.e. the velocity vector is initialised to zero for each virtual bat. We have also incorporated this attribute in BAPSO. Thus, the BAPSO algorithm can be mathematically defined as follows:

$$v'_i = r \cdot v + r_1 c_1 \cdot (p_i^b - p_i) + r_2 c_2 \cdot (g^b - p_i), \quad (5)$$

$$p'_i = p_i + v'_i, \quad (6)$$

2.4. Grey wolf inspired particle swarm optimisation (GWPSO)

GWO, proposed by Mirjalili et al. (2014) is another recently proposed nature-inspired metaheuristic. This is based on the social hierarchy and hunting behaviour of grey wolf packs. Grey wolves are apex predators, and they hunt in packs or groups. In each group,

there is a leader wolf known as the alpha, and the next level of hierarchy contains two to three wolves known as betas. The next level comprises of the deltas, and the remaining are known as the omegas. We have incorporated this hierarchical approach in the traditional PSO. In the proposed GWPSO, in each iteration, the particles memorise the second and the third global best solutions, i.e. g_2^b and g_3^b , in addition to the global best solution g_1^b . Subsequently, the global best solution used for the calculation of the next generation of solutions according to Eq. (3) has been calculated as:

$$g^b = \frac{g_1^b + g_2^b + g_3^b}{3}. \quad (7)$$

2.5. Artificial bee colony (ABC)

ABC, proposed by Karaboga and Basturk (2007) simulates the natural foraging behaviour of honey bees. In ABC, there are three types of virtual bees, namely, employed bees, onlooker bees, and scout bees. The three types of bees share information among themselves to find the best solution. An artificial bee searching for a solution is known as an employed bee. An artificial bee observing the search of the employed bees and subsequently deciding upon which portion of the search space to explore is known as an onlooker bee. Once a solution is rejected, a virtual bee becomes unemployed. It then carries out a random search in the solution space and is known as a scout bee.

In ABC, the number of employed bees is same as the number of possible solutions, thus allotting one bee to one food source. Additionally, employed bees constitute half of the colony with the other half being formed by the onlooker bees. Once a solution cannot be further improved, an employed bee is exhausted, and she becomes a scout bee. An onlooker bee selects a solution found by an employed bee according to a probability, as defined below:

$$p_i = \exp\left(\frac{-1}{\rho \cdot f_i}\right), \quad (8)$$

where ρ is a control parameter (Babayigit and Ozdemir, 2012) used in the algorithm and f_i is the fitness of each solution normalised in $[0, 1]$. Then, the onlooker bee calculates the solution for the next generation according to:

$$x_i^{t+1} = x_{best}^t + \phi_i \cdot (x_{best}^t - x_i^t), \quad (9)$$

where x_{best}^t is the best solution of the current generation and x_i^t is the i th solution being exploited by an artificial bee. The combination of Eqs. (8) and (9) makes ABC a Robin Hood of algorithms that takes from the rich and gives to the poor. Essentially, the worst fitness valued solution gets the best chance for local search by Eq. (8), while the best solution in the current generation is used to modify all other solutions in the generation to find new solutions for the next generation by Eq. (9).

The No Free Lunch (NFL) theorem (Wolpert and Macready, 1997) affirms that no particular metaheuristic is the best suited for all categories of optimisation problems. Hence, identifying more suitable and efficient optimisation techniques for the accurate inference of GRNs is still an open problem for researchers. This provides motivation for this research, where we have studied the performance of different metaheuristic algorithms and attempted to combine their strengths for the novel GRN construction scheme.

3. Methods

In this section, we have explained, in detail, our proposed methodology for reverse engineering GRNs from time-series gene expression datasets. Researchers have employed a decoupling

Table 1
Experimental setup.

Network	No. of Regulations	No. of Datasets	Maximum No. of Generations	Specifications of Machine
Yeast IMRA	6			
<i>E. coli</i> SOS DNA Repair	9			Intel Core i7
10-gene DREAM3 Challenge	11			32 GB RAM
10-gene DREAM4 Challenge	16	4	10000	Windows 10
15-gene extracted from GNW	19			Matlab 2016a
20-gene extracted from GNW	24			

Table 2
Experimental results of the proposed methodology of model/technique combination for the *Saccharomyces cerevisiae* IMRA network for $\alpha = 0.8$.

Switch On													
Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 01							Dataset 02					
PSO (1)	2	8	0.33	0.58	0.52	0.25	PSO (1)	2	6	0.33	0.68	0.60	0.29
BAPSO (2)	2	7	0.33	0.63	0.56	0.27	BAPSO (2)	3	7	0.50	0.63	0.60	0.38
GWPSO (3)	2	6	0.33	0.68	0.60	0.29	GWPSO (3)	3	7	0.50	0.63	0.60	0.38
ABC (4)	0	4	0.00	0.79	0.60	0.00	ABC (4)	0	3	0.00	0.84	0.64	0.00
(1)+(2)+(3)+(4)	0	4	0.00	0.79	0.60	0.00	(1)+(2)+(3)+(4)	0	3	0.00	0.84	0.64	0.00
Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 03							Dataset 04					
PSO (1)	3	7	0.50	0.63	0.60	0.38	PSO (1)	2	8	0.33	0.58	0.52	0.25
BAPSO (2)	2	6	0.33	0.68	0.60	0.29	BAPSO (2)	2	8	0.33	0.58	0.52	0.25
GWPSO (3)	2	7	0.33	0.63	0.56	0.27	GWPSO (3)	2	7	0.33	0.63	0.56	0.27
ABC (4)	1	4	0.17	0.79	0.64	0.18	ABC (4)	0	5	0.00	0.74	0.56	0.00
(1)+(2)+(3)+(4)	1	4	0.17	0.79	0.64	0.18	(1)+(2)+(3)+(4)	0	4	0.00	0.79	0.60	0.00
Switch Off													
Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 01							Dataset 02					
PSO (1)	2	7	0.33	0.63	0.56	0.27	PSO (1)	2	7	0.33	0.63	0.56	0.27
BAPSO (2)	1	7	0.17	0.63	0.52	0.14	BAPSO (2)	3	6	0.50	0.68	0.64	0.40
GWPSO (3)	2	8	0.33	0.58	0.52	0.25	GWPSO (3)	2	7	0.33	0.63	0.56	0.27
ABC (4)	1	3	0.17	0.84	0.68	0.20	ABC (4)	2	2	0.33	0.89	0.76	0.40
(1)+(2)+(3)+(4)	1	3	0.17	0.84	0.68	0.20	(1)+(2)+(3)+(4)	1	2	0.17	0.89	0.72	0.22
Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 03							Dataset 04					
PSO (1)	1	6	0.17	0.68	0.56	0.15	PSO (1)	2	7	0.33	0.63	0.56	0.27
BAPSO (2)	1	8	0.17	0.58	0.48	0.13	BAPSO (2)	3	7	0.50	0.63	0.60	0.38
GWPSO (3)	1	6	0.17	0.68	0.56	0.15	GWPSO (3)	3	7	0.50	0.63	0.60	0.38
ABC (4)	2	3	0.33	0.84	0.72	0.36	ABC (4)	2	5	0.33	0.74	0.64	0.31
(1)+(2)+(3)+(4)	1	2	0.17	0.89	0.72	0.22	(1)+(2)+(3)+(4)	1	5	0.17	0.74	0.60	0.17

scheme (Kentzogloukis and Poole, 2012), where the reverse engineering problem has been divided into two problems: (i) search for a suitable, biologically plausible GRN, and (ii) proper training of the corresponding RNN model parameters, and we have implemented this approach.

Let us first consider the first half of the decoupled problem. Bolouri and Davidson (2002) have stated that on an average, a gene is regulated by four to eight other genes. Here, we have applied our proposed methodology on 5-gene, 8-gene, 10-gene, 15-gene, and 20-gene networks for analysis. Therefore, we have assumed the maximum in-degree for a gene (i.e. the maximum number of regulations on a gene) to be four. This assumption reduces the discrete search space of probable GRNs, significantly. Moreover, with a

maximum in-degree of four, there can be a maximum of $\binom{N}{4}$ number of possible candidate GRN structures, where N is the number of genes in the given GRN. This reduces the overall search space from 2^N to $\binom{N}{4}$. Furthermore, since all possible combination of regulators are being considered, the biological plausibility of the candidate GRNs are likely to be maintained to the maximum possible extent.

Next, let us examine the problem of training the RNN model parameters. If there are N genes in a GRN, then for each gene, $N+2$ parameters are to be trained. Thus, the dimension of the optimisation problem is $N \times (N+2)$. This becomes computationally expensive for larger values of N . Biologically, GRNs are known to be sparse (D'haeseleer and Forrest, 2000), i.e. most of the values

Table 3

Experimental results for the *dataset ensemble* approach, and the *proposed methodology of model/technique combination* applied on it for the *Saccharomyces cerevisiae* IMRA network.

Switch On: All Datasets Combined													
Methods	$\alpha = 0.80$						Methods	$\alpha = 0.20$					
	TP	FP	S_n	S_p	ACC	F-Score		TP	FP	S_n	S_p	ACC	F-Score
PSO (1)	1	2	0.17	0.89	0.72	0.22	PSO (1)	4	16	0.67	0.16	0.28	0.31
BAPSO (2)	1	3	0.17	0.84	0.68	0.20	BAPSO (2)	4	14	0.67	0.26	0.36	0.33
GWPSO (3)	1	2	0.17	0.89	0.72	0.22	GWPSO (3)	3	15	0.50	0.21	0.28	0.25
ABC (4)	0	1	0.00	0.95	0.72	0.00	ABC (4)	4	17	0.67	0.11	0.24	0.30
(1)+(2)+(3)+(4)	0	1	0.00	0.95	0.72	0.00	(1)+(2)+(3)+(4)	3	14	0.50	0.26	0.32	0.26

Switch Off: All Datasets Combined													
Methods	$\alpha = 0.80$						Methods	$\alpha = 0.20$					
	TP	FP	S_n	S_p	ACC	F-Score		TP	FP	S_n	S_p	ACC	F-Score
PSO (1)	0	1	0.00	0.95	0.72	0.00	PSO (1)	4	17	0.67	0.11	0.24	0.30
BAPSO (2)	0	1	0.00	0.95	0.72	0.00	BAPSO (2)	4	17	0.67	0.11	0.24	0.30
GWPSO (3)	0	1	0.00	0.95	0.72	0.00	GWPSO (3)	4	17	0.67	0.11	0.24	0.30
ABC (4)	0	0	0.00	1.00	0.76	0.00	ABC (4)	4	18	0.67	0.05	0.20	0.29
(1)+(2)+(3)+(4)	0	0	0.00	1.00	0.76	0.00	(1)+(2)+(3)+(4)	4	16	0.67	0.16	0.28	0.31

Table 4

Experimental results of *all possible combinations of models/techniques* for the *Saccharomyces cerevisiae* IMRA network (*switch on* experiment) for each individual dataset. (1) PSO, (2) BAPSO, (3) GWPSO, and (4) ABC.

Switch On													
Method Combinations	TP	FP	S_n	S_p	ACC	F-Score	Method Combinations	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 01							Dataset 02					
(1)+(2)	2	7	0.33	0.63	0.56	0.27	(1)+(2)	2	6	0.33	0.68	0.60	0.29
(1)+(3)	2	6	0.33	0.68	0.60	0.29	(1)+(3)	2	6	0.33	0.68	0.60	0.29
(1)+(4)	0	4	0.00	0.79	0.60	0.00	(1)+(4)	0	3	0.00	0.84	0.64	0.00
(2)+(3)	2	6	0.33	0.68	0.60	0.29	(2)+(3)	3	7	0.50	0.63	0.60	0.38
(2)+(4)	0	4	0.00	0.79	0.60	0.00	(2)+(4)	0	3	0.00	0.84	0.64	0.00
(3)+(4)	0	4	0.00	0.79	0.60	0.00	(3)+(4)	0	3	0.00	0.84	0.64	0.00
(1)+(2)+(3)	2	6	0.33	0.68	0.60	0.29	(1)+(2)+(3)	2	6	0.33	0.68	0.60	0.29
(1)+(2)+(4)	0	4	0.00	0.79	0.60	0.00	(1)+(2)+(4)	0	3	0.00	0.84	0.64	0.00
(1)+(3)+(4)	0	4	0.00	0.79	0.60	0.00	(1)+(3)+(4)	0	3	0.00	0.84	0.64	0.00
(2)+(3)+(4)	0	4	0.00	0.79	0.60	0.00	(2)+(3)+(4)	0	3	0.00	0.84	0.64	0.00
(1)+(2)+(3)+(4)	0	4	0.00	0.79	0.60	0.00	(1)+(2)+(3)+(4)	0	3	0.00	0.84	0.64	0.00
Method Combinations	TP	FP	S_n	S_p	ACC	F-Score	Method Combinations	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 03							Dataset 04					
(1)+(2)	2	6	0.33	0.68	0.60	0.29	(1)+(2)	2	8	0.33	0.58	0.52	0.25
(1)+(3)	2	7	0.33	0.63	0.56	0.27	(1)+(3)	2	7	0.33	0.63	0.56	0.27
(1)+(4)	1	4	0.17	0.79	0.64	0.18	(1)+(4)	0	5	0.00	0.74	0.56	0.00
(2)+(3)	2	6	0.33	0.68	0.60	0.29	(2)+(3)	2	7	0.33	0.63	0.56	0.27
(2)+(4)	1	4	0.17	0.79	0.64	0.18	(2)+(4)	0	5	0.00	0.74	0.56	0.00
(3)+(4)	1	4	0.17	0.79	0.64	0.18	(3)+(4)	0	4	0.00	0.79	0.60	0.00
(1)+(2)+(3)	2	6	0.33	0.68	0.60	0.29	(1)+(2)+(3)	2	7	0.33	0.63	0.56	0.27
(1)+(2)+(4)	1	4	0.17	0.79	0.64	0.18	(1)+(2)+(4)	0	5	0.00	0.74	0.56	0.00
(1)+(3)+(4)	1	4	0.17	0.79	0.64	0.18	(1)+(3)+(4)	0	4	0.00	0.79	0.60	0.00
(2)+(3)+(4)	1	4	0.17	0.79	0.64	0.18	(2)+(3)+(4)	0	4	0.00	0.79	0.60	0.00
(1)+(2)+(3)+(4)	1	4	0.17	0.79	0.64	0.18	(1)+(2)+(3)+(4)	0	4	0.00	0.79	0.60	0.00

of w_{ij} (in Eq. (1)) are zero. However, even this seemingly advantageous restriction cannot reduce the computational load significantly. Hence, researchers proposed to decompose the $N \times (N+2)$ dimensional optimisation problem into N sub-problems of $(N+2)$ dimensions each. Each gene, thus, can be studied separately, and the respective $(N+2)$ RNN model parameters trained in each case. Thus, in this work, the fitness/objective function for the meta-heuristic techniques has been redefined as:

$$er_i = \frac{1}{T} \sum_1^T (x_i(t) - \tilde{x}_i(t))^2. \quad (10)$$

In this work, we have represented a GRN by a directed graph $G = (V, E)$, where V and E contain all the nodes (genes) and the edges (relationship among the genes), respectively. For computational purposes, G has been denoted as $G = [g_{ij}]_{N \times N}$, where N is the number of genes in the GRN. The value of the element g_{ij} is 0 or 1 subject to the absence or presence, of an edge from node j to node i , respectively.

Due to the stochastic nature of the training algorithms employed, the inferred GRNs are likely to vary in their structures with each independent experiment for a given network. Thus, we have implemented a collaborative training scheme, where we have constructed L independent GRNs for each of the L independent exper-

Table 5

Experimental results of all possible combinations of models/techniques for the *Saccharomyces cerevisiae* IMRA network (switch off experiment) for each individual dataset. (1) PSO, (2) BAPSO, (3) GWPSO, and (4) ABC.

Method Combinations	Switch Off						Method Combinations	Dataset 02						
	Dataset 01							Dataset 02						
	TP	FP	S_n	S_p	ACC	F-Score		TP	FP	S_n	S_p	ACC	F-Score	
(1)+(2)	1	7	0.17	0.63	0.52	0.14	(1)+(2)	2	6	0.33	0.68	0.60	0.29	
(1)+(3)	2	7	0.33	0.63	0.56	0.27	(1)+(3)	2	7	0.33	0.63	0.56	0.27	
(1)+(4)	1	3	0.17	0.84	0.68	0.20	(1)+(4)	1	2	0.17	0.89	0.72	0.22	
(2)+(3)	1	7	0.17	0.63	0.52	0.14	(2)+(3)	2	6	0.33	0.68	0.60	0.29	
(2)+(4)	1	3	0.17	0.84	0.68	0.20	(2)+(4)	2	2	0.33	0.89	0.76	0.40	
(3)+(4)	1	3	0.17	0.84	0.68	0.20	(3)+(4)	1	2	0.17	0.89	0.72	0.22	
(1)+(2)+(3)	1	7	0.17	0.63	0.52	0.14	(1)+(2)+(3)	2	6	0.33	0.68	0.60	0.29	
(1)+(2)+(4)	1	3	0.17	0.84	0.68	0.20	(1)+(2)+(4)	1	2	0.17	0.89	0.72	0.22	
(1)+(3)+(4)	1	3	0.17	0.84	0.68	0.20	(1)+(3)+(4)	1	2	0.17	0.89	0.72	0.22	
(2)+(3)+(4)	1	3	0.17	0.84	0.68	0.20	(2)+(3)+(4)	1	2	0.17	0.89	0.72	0.22	
(1)+(2)+(3)+(4)	1	3	0.17	0.84	0.68	0.20	(1)+(2)+(3)+(4)	1	2	0.17	0.89	0.72	0.22	
Method Combinations	Dataset 03						Method Combinations	Dataset 04						
	TP	FP	S_n	S_p	ACC	F-Score		TP	FP	S_n	S_p	ACC	F-Score	
	1	6	0.17	0.68	0.56	0.15	(1)+(2)	2	7	0.33	0.63	0.56	0.27	
(1)+(3)	1	6	0.17	0.68	0.56	0.15	(1)+(3)	2	7	0.33	0.63	0.56	0.27	
(1)+(4)	1	2	0.17	0.89	0.72	0.22	(1)+(4)	1	5	0.17	0.74	0.60	0.17	
(2)+(3)	1	6	0.17	0.68	0.56	0.15	(2)+(3)	3	7	0.50	0.63	0.60	0.38	
(2)+(4)	1	3	0.17	0.84	0.68	0.20	(2)+(4)	2	5	0.33	0.74	0.64	0.31	
(3)+(4)	1	2	0.17	0.89	0.72	0.22	(3)+(4)	2	5	0.33	0.74	0.64	0.31	
(1)+(2)+(3)	1	6	0.17	0.68	0.56	0.15	(1)+(2)+(3)	2	7	0.33	0.63	0.56	0.27	
(1)+(2)+(4)	1	2	0.17	0.89	0.72	0.22	(1)+(2)+(4)	1	5	0.17	0.74	0.60	0.17	
(1)+(3)+(4)	1	2	0.17	0.89	0.72	0.22	(1)+(3)+(4)	1	5	0.17	0.74	0.60	0.17	
(2)+(3)+(4)	1	2	0.17	0.89	0.72	0.22	(2)+(3)+(4)	2	5	0.33	0.74	0.64	0.31	
(1)+(2)+(3)+(4)	1	2	0.17	0.89	0.72	0.22	(1)+(2)+(3)+(4)	1	5	0.17	0.74	0.60	0.17	

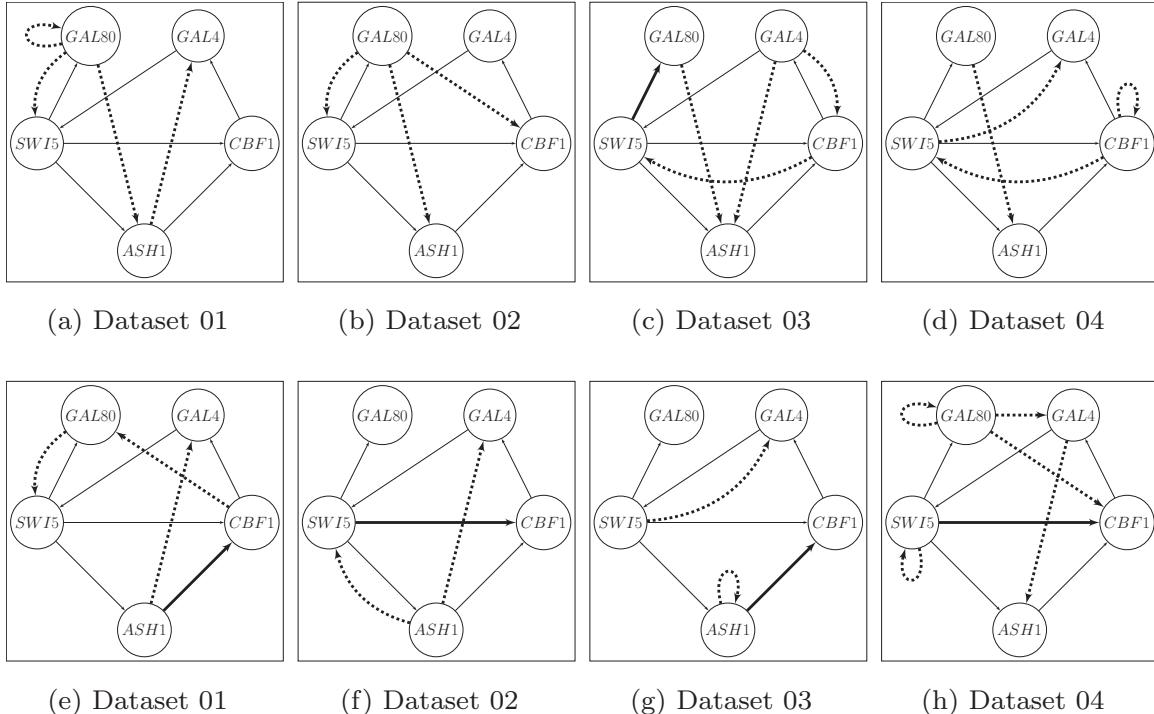


Fig. 2. The structure of the Yeast IMRA network. The thick edges represent those regulations that have been predicted correctly i.e. TPs. The thin edges represent those regulations that could not be predicted, i.e. FNs. The dashed edges represent the spurious relations that have been predicted by our model, i.e. FPs.

iments. Subsequently, we have devised a selection technique based on a plausibility score ps_{ij} , assigned to each edge of the inferred GRN as:

$$ps_{ij} = \frac{1}{L} \sum_1^L g_{ij}^p, \quad (11)$$

where $g_{ij}^p \in G^p$ and G^p denotes the inferred GRN in each L experiment (n/a). We have constructed the final inferred GRNs, $G^F = [g_{ij}^F]_{N \times N}$, where N is the number of genes, based on ps_{ij} , for each

of the three experiments, as:

$$g_{ij}^f = \begin{cases} 0, & \text{if } ps_{ij} \geq \alpha \\ 1, & \text{otherwise} \end{cases}, \quad (12)$$

where α has been defined as a threshold of the plausibility score, for inclusion of a particular edge in the final inferred GRN; g_{ij}^f denotes the presence or absence of an edge in the GRN, and it does not represent the type of relationship amongst the nodes (activation or repression).

The novelty of this research endeavour is in the final GRN construction strategy based on the results of the four swarm intelligence algorithms used; i.e. the four different inferred GRNs G_{PSO}^F , G_{BAPSO}^F , G_{GWPSON}^F , and G_{ABC}^F obtained from PSO, BAPSO, GWPSON, and ABC, respectively. We have superimposed all the predicted GRNs and have kept only those edges, which are common to all the structures, to construct the final GRN. This filters out many of the FPs while keeping most of the predicted TPs intact.

This can be explained based on the fact that GRNs are sparse. Thus, there are very few edges that can be identified as TPs. On the other hand, the number of probable incorrect predictions is equal to (N^2 - the number of actual edges present), where N is the number of genes in the network. Thus, it is *more probable* that the same TP is identified by all the four metaheuristic techniques. Similarly, there is a *lesser probability* that all the techniques identify the same FP, and this probability further goes down as N increases. Therefore, many of the incorrectly predicted regulations usually differ in their locations in the four inferred GRNs. They are thus, eliminated during the superimposition and subsequent filtering processes. On the other hand, majority of the identified TPs are likely to be fixed in their locations and survive the elimination process.

4. Experimental results and discussion

We have implemented the proposed methodology on the following types of datasets:

1. Two *in vivo* cases: (i) *Saccharomyces cerevisiae* IMRA network, and (ii) the *Escherichia coli* SOS DNA Repair network;
2. Four *in silico* cases: (i) a 10-gene DREAM3 Challenge network, (ii) a 10-gene DREAM4 Challenge network, (iii) a 15-gene network extracted from GNW, and finally, (iv) a 20-gene network extracted from GNW.

All specifications of the experimental setups have been given in [Table 1](#).

We have used certain metrics to evaluate the performance of the proposed algorithm. We have defined them, next. An edge in the final GRN can be categorised as (a) a True Positive (TP), if an existing regulation has been correctly identified, (b) a False Positive (FP), if a non-existent regulation has been identified as existing in the inferred GRN, (c) a True Negative (TN), if a non-existent regulation has been correctly identified, and (d) a False Negative (FN), if an existing regulation has been identified as non-existent in the inferred GRN. The metrics that have been used for evaluation of the proposed methodology are as follows:

$$\text{Sensitivity, } S_n = \frac{TP}{TP + FN}, \quad (13)$$

$$\text{Specificity, } S_p = \frac{TN}{TN + FP}, \quad (14)$$

$$\text{Accuracy, } ACC = \frac{TP + TN}{TP + FP + FN + TN}, \quad (15)$$

$$F\text{-Score} = \frac{2TP}{2TP + FP + FN}. \quad (16)$$

4.1. *Saccharomyces cerevisiae* IMRA network

This is an *in vivo* benchmark dataset proposed by [Cantone et al. \(2009\)](#). The network contains five genes, SWI5, ASH1, CBF1, GAL4, and GAL80, and six interactions amongst them. The authors performed nine experiments: *five switch on* experiments, where a shift of the yeast samples from glucose to galactose-raffinose-containing medium was done; and *four switch off* experiments where a shift from galactose-raffinose- to glucose-containing medium was done.

We have experimented on all the four datasets of the *switch off* experiment. However, we have left out one dataset from the *switch on* experiment because it had too few time-points, and also to maintain parity with the other experiments performed in this work.

We have presented the results in [Tables 2–5](#). We have also presented the inferred networks from each of the datasets in [Fig. 2](#). [Table 2](#) shows the reduction achieved in the number of FPs by the proposed methodology (combining all the metaheuristic techniques) for each of the four datasets for both the *switch on* and *switch off* experiments. Due to the *bad performance* of ABC in the case of the *in vivo switch on* dataset, compared to the other techniques, the FP reduction has been slightly hampered in this particular case. Leaving ABC out, and using only BAPSO, GWPSON, and PSO, the results slightly improve as can be seen in [Table 4](#).

In [Table 3](#), we have presented the results when all the four datasets have been combined i.e. *dataset ensemble* approach, and it is observed that combining four datasets and using a strict threshold of $\alpha = 0.8$, all TPs and FPs get filtered out. This is expected because the number of TPs inferred from each dataset is low as shown in [Table 2](#), especially by ABC. To rectify this, we have to provide more information to the proposed methodology before the filtering process, and that can be achieved by lowering the threshold to $\alpha = 0.2$.

The results with $\alpha = 0.2$ has also been shown in [Table 3](#). Here, it can be clearly observed that both the number of TPs and FPs increase, but our proposed methodology is still able to reduce the enhanced number of FPs inferred. For the *switch on* case, the specificity increases from a minimum of 0.11 (for ABC) to 0.26, an increase of 136.4%. For the *switch off* case, the specificity increases from a minimum of 0.05 (for ABC) to 0.16, again showing an *increase of more than two-folds*. The accuracy also increases from a minimum of 0.20 (for ABC) to 0.28.

Finally, results for all possible combinations of the techniques for each dataset have been given separately in [Tables 4](#) and [5](#) for the *switch on* and *switch off* experiments, respectively. Also, in [Table 6](#), we have presented the same for the *dataset ensemble* approach.

4.2. *Escherichia coli* SOS DNA repair network

Next, we have implemented the proposed methodology for the reverse engineering of GRNs from another *in vivo* benchmark, the real-world experimental datasets of *Escherichia coli*. The datasets encapsulate the dynamics of the transcriptional network involved in the SOS DNA Repair mechanism of *E. coli*. [Ronen et al. \(2002\)](#) experimentally studied eight genes largely involved in the SOS DNA Repair system, namely, uvrA, uvrD, uvrY, umuDC, ruvA, polB, recA, and lexA.

The authors ([Ronen et al., 2002](#)) performed four experiments, and therefore, there are four such *in vivo* datasets. In each experiment, expression data of the eight genes has been collected for 50 time-points at a temporal resolution of six minutes. The gene expression value for the first time-point in each dataset is zero. Hence, we have omitted that from the inference process. Also, we have normalised the expression data. These are one of the most

Table 6

Experimental results of all possible combinations of models/techniques applied upon the dataset ensemble approach for the *Saccharomyces cerevisiae* IMRA network for each individual dataset. (1) PSO, (2) BAPSO, (3) GWPSO, and (4) ABC.

Switch On: All Datasets Combined													
Method Combinations	$\alpha = 0.80$					Method Combinations	$\alpha = 0.20$						
	TP	FP	S_n	S_p	ACC	F-Score	TP	FP	S_n	S_p	ACC	F-Score	
(1)+(2)	1	2	0.17	0.89	0.72	0.22	(1)+(2)	4	14	0.67	0.26	0.36	0.33
(1)+(3)	1	1	0.17	0.95	0.76	0.25	(1)+(3)	3	15	0.50	0.21	0.28	0.25
(1)+(4)	0	1	0.00	0.95	0.72	0.00	(1)+(4)	4	16	0.67	0.16	0.28	0.31
(2)+(3)	1	2	0.17	0.89	0.72	0.22	(2)+(3)	3	14	0.50	0.26	0.32	0.26
(2)+(4)	0	1	0.00	0.95	0.72	0.00	(2)+(4)	4	14	0.67	0.26	0.36	0.33
(3)+(4)	0	1	0.00	0.95	0.72	0.00	(3)+(4)	3	15	0.50	0.21	0.28	0.25
(1)+(2)+(3)	1	1	0.17	0.95	0.76	0.25	(1)+(2)+(3)	3	14	0.50	0.26	0.32	0.26
(1)+(2)+(4)	0	1	0.00	0.95	0.72	0.00	(1)+(2)+(4)	4	14	0.67	0.26	0.36	0.33
(1)+(3)+(4)	0	1	0.00	0.95	0.72	0.00	(1)+(3)+(4)	3	15	0.50	0.21	0.28	0.25
(2)+(3)+(4)	0	1	0.00	0.95	0.72	0.00	(2)+(3)+(4)	3	14	0.50	0.26	0.32	0.26
(1)+(2)+(3)+(4)	0	1	0.00	0.95	0.72	0.00	(1)+(2)+(3)+(4)	3	14	0.50	0.26	0.32	0.26
Switch Off: All Datasets Combined													
Method Combinations	$\alpha = 0.80$					Method Combinations	$\alpha = 0.20$						
	TP	FP	S_n	S_p	ACC	F-Score	TP	FP	S_n	S_p	ACC	F-Score	
(1)+(2)	0	1	0.00	0.95	0.72	0.00	(1)+(2)	4	17	0.67	0.11	0.24	0.30
(1)+(3)	0	1	0.00	0.95	0.72	0.00	(1)+(3)	4	17	0.67	0.11	0.24	0.30
(1)+(4)	0	0	0.00	1.00	0.76	0.00	(1)+(4)	4	16	0.67	0.16	0.28	0.31
(2)+(3)	0	1	0.00	0.95	0.72	0.00	(2)+(3)	4	17	0.67	0.11	0.24	0.30
(2)+(4)	0	0	0.00	1.00	0.76	0.00	(2)+(4)	4	16	0.67	0.16	0.28	0.31
(3)+(4)	0	0	0.00	1.00	0.76	0.00	(3)+(4)	4	16	0.67	0.16	0.28	0.31
(1)+(2)+(3)	0	1	0.00	0.95	0.72	0.00	(1)+(2)+(3)	4	17	0.67	0.11	0.24	0.30
(1)+(2)+(4)	0	0	0.00	1.00	0.76	0.00	(1)+(2)+(4)	4	16	0.67	0.16	0.28	0.31
(1)+(3)+(4)	0	0	0.00	1.00	0.76	0.00	(1)+(3)+(4)	4	16	0.67	0.16	0.28	0.31
(2)+(3)+(4)	0	0	0.00	1.00	0.76	0.00	(2)+(3)+(4)	4	16	0.67	0.16	0.28	0.31
(1)+(2)+(3)+(4)	0	0	0.00	1.00	0.76	0.00	(1)+(2)+(3)+(4)	4	16	0.67	0.16	0.28	0.31

Table 7

Experimental results of the proposed methodology of model/technique combination for the *Escherichia coli* SOS DNA Repair network for $\alpha = 0.8$, and comparison with Kentzogloukis and Poole (2012).

Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 01							Dataset 02					
eDSF [17]	3	10	0.33	0.82	0.75	0.27	eDSF [17]	8	5	0.89	0.91	0.91	0.73
PSO (1)	7	7	0.78	0.87	0.86	0.61	PSO (1)	7	13	0.78	0.76	0.77	0.48
BAPSO (2)	7	13	0.78	0.76	0.77	0.48	BAPSO (2)	9	15	1.00	0.73	0.77	0.55
GWPSO (3)	7	10	0.78	0.82	0.81	0.54	GWPSO (3)	7	15	0.78	0.73	0.73	0.45
ABC (4)	8	17	0.89	0.69	0.72	0.47	ABC (4)	9	14	1.00	0.75	0.78	0.56
(1)+(2)+(3)+(4)	7	7	0.78	0.87	0.86	0.61	(1)+(2)+(3)+(4)	6	12	0.67	0.78	0.77	0.44
Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 03							Dataset 04					
eDSF [17]	4	9	0.44	0.84	0.78	0.36	eDSF [17]	0	9	0.00	0.84	0.72	0.00
PSO (1)	8	10	0.89	0.82	0.83	0.59	PSO (1)	6	11	0.67	0.80	0.78	0.46
BAPSO (2)	6	13	0.67	0.76	0.75	0.43	BAPSO (2)	6	10	0.67	0.82	0.80	0.48
GWPSO (3)	6	11	0.67	0.80	0.78	0.46	GWPSO (3)	6	11	0.67	0.80	0.78	0.46
ABC (4)	7	20	0.78	0.64	0.66	0.39	ABC (4)	7	20	0.78	0.64	0.66	0.39
(1)+(2)+(3)+(4)	5	0	0.56	1.00	0.94	0.71	(1)+(2)+(3)+(4)	6	9	0.67	0.84	0.81	0.50

Table 8

Experimental results for the dataset ensemble approach, and the proposed methodology of model/technique combination applied on it for the *Escherichia coli* SOS DNA Repair network.

All Datasets Combined													
Methods	$\alpha = 0.80$						Methods	$\alpha = 0.20$					
	TP	FP	S_n	S_p	ACC	F-Score		TP	FP	S_n	S_p	ACC	F-Score
PSO (1)	7	8	0.78	0.85	0.84	0.58	PSO (1)	9	41	1.00	0.25	0.36	0.31
BAPSO (2)	6	6	0.67	0.89	0.86	0.57	BAPSO (2)	9	40	1.00	0.27	0.38	0.31
GWPSO (3)	5	4	0.56	0.93	0.88	0.56	GWPSO (3)	9	41	1.00	0.25	0.36	0.31
ABC (4)	7	4	0.78	0.93	0.91	0.70	ABC (4)	9	37	1.00	0.33	0.42	0.33
(1)+(2)+(3)+(4)	5	1	0.56	0.98	0.92	0.67	(1)+(2)+(3)+(4)	9	26	1.00	0.53	0.59	0.41

Table 9

Experimental results of all possible combinations of models/techniques for the *Escherichia coli* SOS DNA Repair network for each individual dataset. (1) PSO, (2) BAPSO, (3) GWPSO, and (4) ABC.

Method Combinations	TP	FP	S_n	S_p	ACC	F-Score	Method Combinations	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 01							Dataset 02					
(1)+(2)	6	9	0.67	0.84	0.81	0.50	(1)+(2)	5	0	0.56	1.00	0.94	0.71
(1)+(3)	7	9	0.78	0.84	0.83	0.56	(1)+(3)	5	0	0.56	1.00	0.94	0.71
(1)+(4)	7	10	0.78	0.82	0.81	0.54	(1)+(4)	6	0	0.67	1.00	0.95	0.80
(2)+(3)	6	9	0.67	0.84	0.81	0.50	(2)+(3)	7	9	0.78	0.84	0.83	0.56
(2)+(4)	6	10	0.67	0.82	0.80	0.48	(2)+(4)	7	11	0.78	0.80	0.80	0.52
(3)+(4)	7	10	0.78	0.82	0.81	0.54	(3)+(4)	7	9	0.78	0.84	0.83	0.56
(1)+(2)+(3)	6	9	0.67	0.84	0.81	0.50	(1)+(2)+(3)	5	0	0.56	1.00	0.94	0.71
(1)+(2)+(4)	6	9	0.67	0.84	0.81	0.50	(1)+(2)+(4)	5	0	0.56	1.00	0.94	0.71
(1)+(3)+(4)	7	9	0.78	0.84	0.83	0.56	(1)+(3)+(4)	5	0	0.56	1.00	0.94	0.71
(2)+(3)+(4)	6	9	0.67	0.84	0.81	0.50	(2)+(3)+(4)	7	9	0.78	0.84	0.83	0.56
(1)+(2)+(3)+(4)	6	9	0.67	0.84	0.81	0.50	(1)+(2)+(3)+(4)	5	0	0.56	1.00	0.94	0.71
Method Combinations	TP	FP	S_n	S_p	ACC	F-Score	Method Combinations	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 03							Dataset 04					
(1)+(2)	6	14	0.67	0.75	0.73	0.41	(1)+(2)	7	7	0.78	0.87	0.86	0.61
(1)+(3)	6	13	0.67	0.76	0.75	0.43	(1)+(3)	7	7	0.78	0.87	0.86	0.61
(1)+(4)	6	13	0.67	0.76	0.75	0.43	(1)+(4)	7	7	0.78	0.87	0.86	0.61
(2)+(3)	7	15	0.78	0.73	0.73	0.45	(2)+(3)	7	10	0.78	0.82	0.81	0.54
(2)+(4)	8	15	0.89	0.73	0.75	0.50	(2)+(4)	7	13	0.78	0.76	0.77	0.48
(3)+(4)	7	14	0.78	0.75	0.75	0.47	(3)+(4)	7	10	0.78	0.82	0.81	0.54
(1)+(2)+(3)	6	13	0.67	0.76	0.75	0.43	(1)+(2)+(3)	7	7	0.78	0.87	0.86	0.61
(1)+(2)+(4)	6	13	0.67	0.76	0.75	0.43	(1)+(2)+(4)	7	7	0.78	0.87	0.86	0.61
(1)+(3)+(4)	6	12	0.67	0.78	0.77	0.44	(1)+(3)+(4)	7	7	0.78	0.87	0.86	0.61
(2)+(3)+(4)	7	14	0.78	0.75	0.75	0.47	(2)+(3)+(4)	7	10	0.78	0.82	0.81	0.54
(1)+(2)+(3)+(4)	6	12	0.67	0.78	0.77	0.44	(1)+(2)+(3)+(4)	7	7	0.78	0.87	0.86	0.61

Table 10

Experimental results of all possible combinations of models/techniques applied upon the dataset ensemble approach for the *Escherichia coli* SOS DNA Repair network for each individual dataset. (1) PSO, (2) BAPSO, (3) GWPSO, and (4) ABC.

All Datasets Combined													
Method Combinations	$\alpha = 0.80$						Method Combinations	$\alpha = 0.20$					
	TP	FP	S_n	S_p	ACC	F-Score		TP	FP	S_n	S_p	ACC	F-Score
(1)+(2)	5	5	0.56	0.91	0.86	0.53	(1)+(2)	9	33	1.00	0.40	0.48	0.35
(1)+(3)	5	4	0.56	0.93	0.88	0.56	(1)+(3)	9	32	1.00	0.42	0.50	0.36
(1)+(4)	6	2	0.67	0.96	0.92	0.71	(1)+(4)	9	30	1.00	0.45	0.53	0.38
(2)+(3)	5	3	0.56	0.95	0.89	0.59	(2)+(3)	9	35	1.00	0.36	0.45	0.34
(2)+(4)	6	1	0.67	0.98	0.94	0.75	(2)+(4)	9	32	1.00	0.42	0.50	0.36
(3)+(4)	5	2	0.56	0.96	0.91	0.63	(3)+(4)	9	32	1.00	0.42	0.50	0.36
(1)+(2)+(3)	5	3	0.56	0.95	0.89	0.59	(1)+(2)+(3)	9	29	1.00	0.47	0.55	0.38
(1)+(2)+(4)	5	1	0.56	0.98	0.92	0.67	(1)+(2)+(4)	9	28	1.00	0.49	0.56	0.39
(1)+(3)+(4)	5	2	0.56	0.96	0.91	0.63	(1)+(3)+(4)	9	27	1.00	0.51	0.58	0.40
(2)+(3)+(4)	5	1	0.56	0.98	0.92	0.67	(2)+(3)+(4)	9	30	1.00	0.45	0.53	0.38
(1)+(2)+(3)+(4)	5	1	0.56	0.98	0.92	0.67	(1)+(2)+(3)+(4)	9	26	1.00	0.53	0.59	0.41

Table 11

Experimental results of the proposed methodology of model/technique combination for the DREAM3 Challenge network for $\alpha = 0.8$.

Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 01							Dataset 02					
PSO (1)	2	17	0.18	0.81	0.74	0.13	PSO (1)	1	13	0.09	0.85	0.77	0.08
BAPSO (2)	2	16	0.18	0.82	0.75	0.14	BAPSO (2)	2	16	0.18	0.82	0.75	0.14
GWPSO (3)	2	17	0.18	0.81	0.74	0.13	GWPSO (3)	1	12	0.09	0.87	0.78	0.08
ABC (4)	2	7	0.18	0.92	0.84	0.20	ABC (4)	2	10	0.18	0.89	0.81	0.17
(1)+(2)+(3)+(4)	2	6	0.18	0.93	0.85	0.21	(1)+(2)+(3)+(4)	1	9	0.09	0.90	0.81	0.10
Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 03							Dataset 04					
PSO (1)	3	15	0.27	0.83	0.77	0.21	PSO (1)	4	15	0.36	0.83	0.78	0.27
BAPSO (2)	3	14	0.27	0.84	0.78	0.21	BAPSO (2)	4	13	0.36	0.85	0.80	0.29
GWPSO (3)	3	14	0.27	0.84	0.78	0.21	GWPSO (3)	4	12	0.36	0.87	0.81	0.30
ABC (4)	1	10	0.09	0.89	0.80	0.09	ABC (4)	3	6	0.27	0.93	0.86	0.30
(1)+(2)+(3)+(4)	1	10	0.09	0.89	0.80	0.09	(1)+(2)+(3)+(4)	3	5	0.27	0.94	0.87	0.32

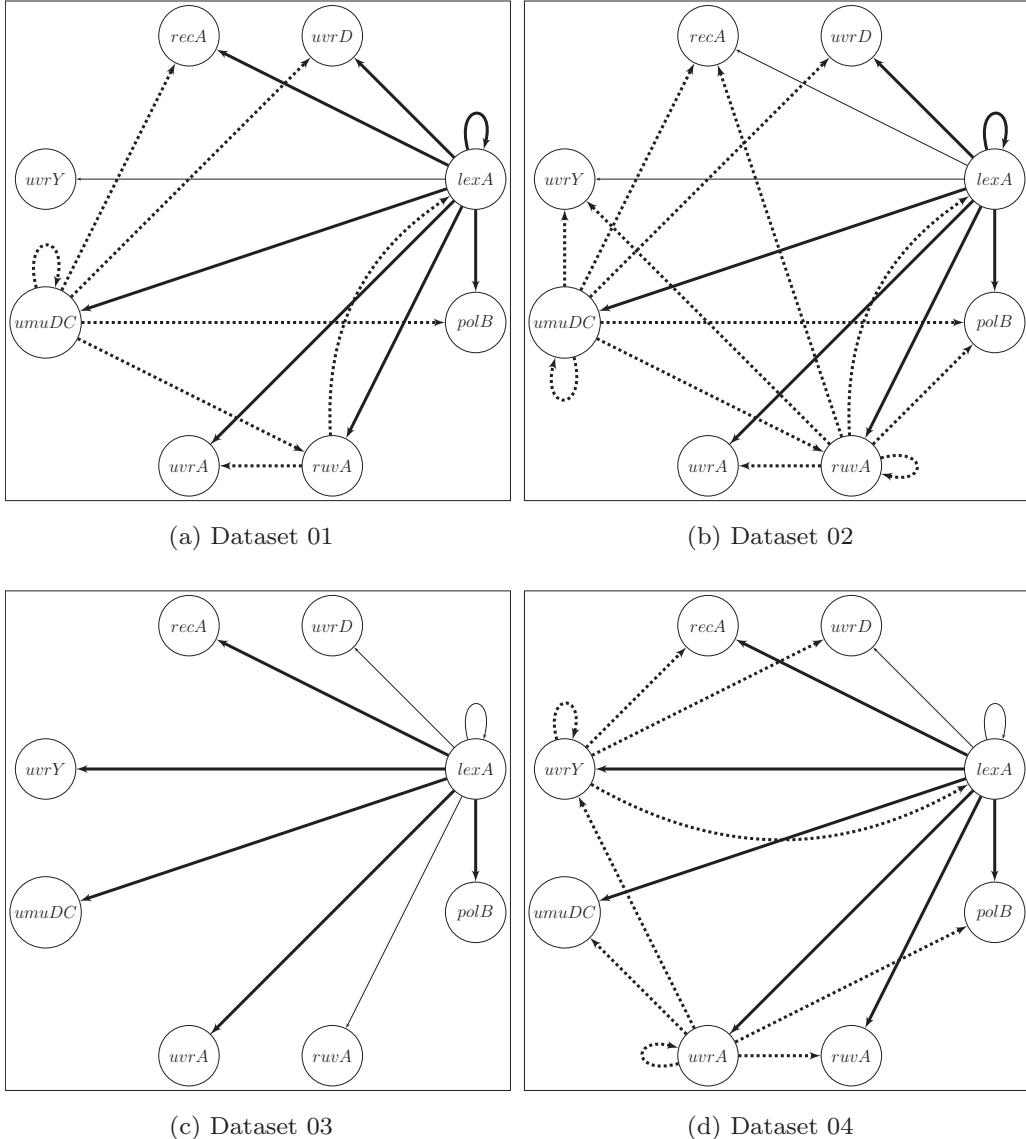


Fig. 3. The structure of the *E. coli* SOS DNA repair network. The thick edges represent those regulations that have been predicted correctly i.e. TPs. The thin edges represent those regulations that could not be predicted, i.e. FN. The dashed edges represent the spurious relations that have been predicted by our model, i.e. FPs.

Table 12

Experimental results for the *dataset ensemble* approach, and the *proposed methodology of model/technique combination* applied on it for the DREAM3 Challenge network.

Methods	All Datasets Combined					
	$\alpha = 0.80$			$\alpha = 0.20$		
	TP	FP	S_n	S_p	ACC	F-Score
PSO (1)	1	0	0.09	1.00	0.90	0.17
BAPSO (2)	1	0	0.09	1.00	0.90	0.17
GWPSO (3)	1	0	0.09	1.00	0.90	0.17
ABC (4)	1	0	0.09	1.00	0.90	0.17
(1)+(2)+(3)+(4)	1	0	0.09	1.00	0.90	0.17
	(1)+(2)+(3)+(4)			5	37	0.45 0.58 0.57 0.19

useful benchmarks regarding research into computational methods for reconstruction of GRNs from temporal expression data.

In Table 7, we have presented the results incorporating PSO, BAPSO, GWPSO and ABC with RNN, where the threshold of the plausibility score $\alpha = 0.8$ has been considered for the construction of the GRN. Kentzoglaniakis and Poole (2012) have also investigated into the four datasets separately, and thus, we have compared our

results with eDSF (Kentzoglaniakis and Poole, 2012). It can be observed that there is a significant decrease in the number of FPs when all the metaheuristics have been combined. The results are better than multiple runs of a single algorithm. The specificity and accuracy of the proposed model are better in most of the cases, compared to the one in Kentzoglaniakis and Poole (2012). The original and predicted network structures have been shown in Fig. 3.

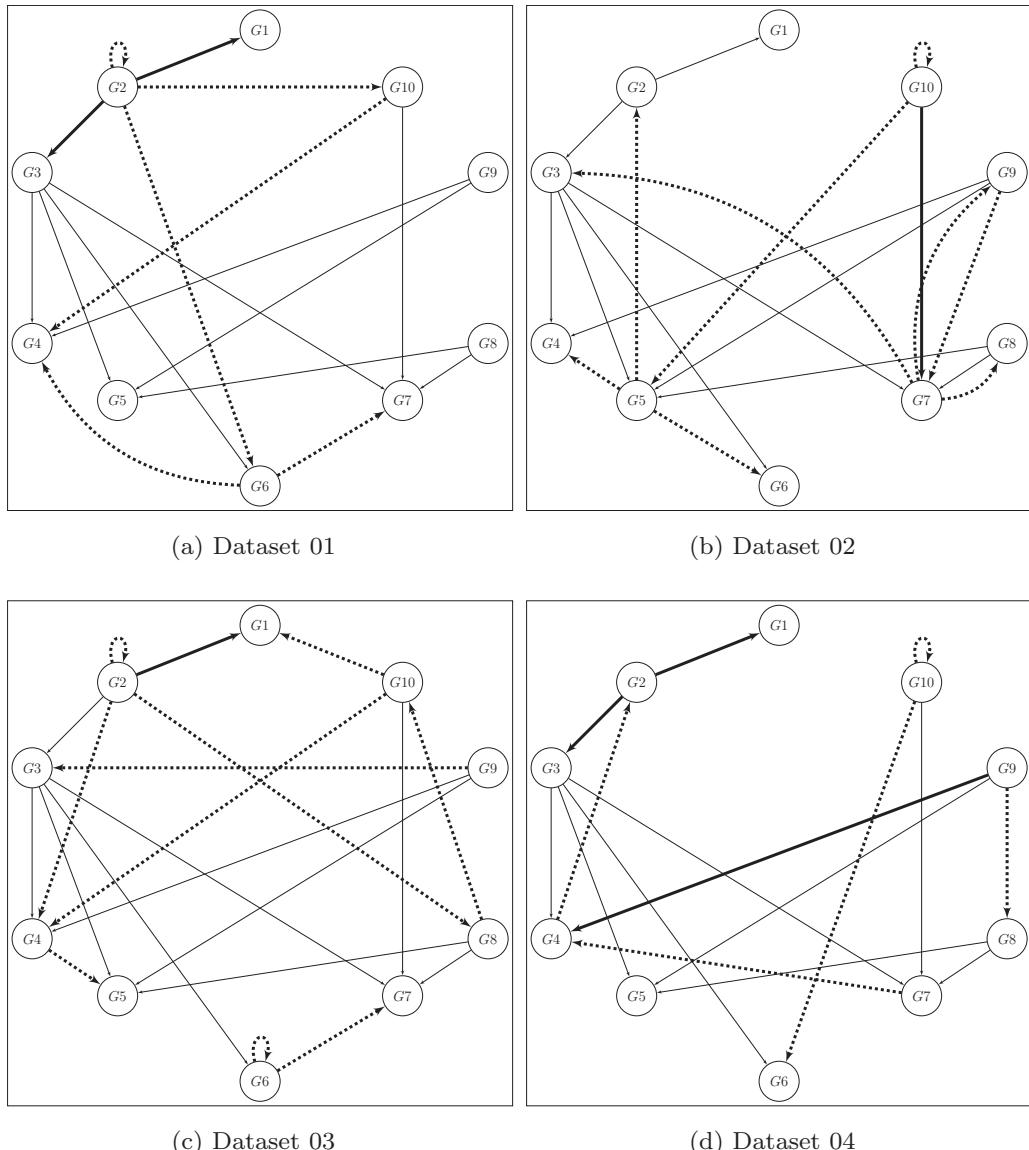


Fig. 4. The structure of 10-gene DREAM3 Challenge network. The thick edges represent those regulations that have been predicted correctly i.e. TPs. The thin edges represent those regulations that could not be predicted, i.e. FNs. The dashed edges represent the spurious relations that have been predicted by our model, i.e. FPs.

To understand the effects of *dataset ensemble*, we have presented in [Table 8](#), the results when the four datasets are combined, for both $\alpha = 0.8$ and $\alpha = 0.2$, in this case also. Also, we have presented the results obtained by our proposed methodology when implemented upon multiple datasets. The results presented clearly show that the proposed methodology still retains the ability to significantly reduce the number of FPs, when multiple datasets have been combined. The *specificity* improves from a minimum of 0.85 to 0.98 and from a minimum of 0.25 to 0.53 for $\alpha = 0.8$ and $\alpha = 0.2$, respectively, when our proposed methodology has been applied to the *dataset ensemble* approach. In other words, there is an increase of 15.3% and 112% for $\alpha = 0.8$ and $\alpha = 0.2$, respectively. Similarly, the *accuracy* increases from a minimum of 0.84 to 0.92 and from a minimum of 0.36 to 0.59 for $\alpha = 0.8$ and $\alpha = 0.2$, respectively. Thus, there is an improvement of 9.5% and 63.9% for $\alpha = 0.8$ and $\alpha = 0.2$, respectively. We would also like to point out that the *sensitivity* remains 1 i.e., no TP is lost by our proposed formalism while reducing the number of FPs (for $\alpha = 0.2$).

Also, we have presented in [Table 9](#), the results of all possible combinations of the techniques for each individual dataset, and for the *dataset ensemble* approach in [Table 10](#).

4.3. 10-gene DREAM3 Challenge network

Next, we have applied the proposed methodology for inferring two *in silico* benchmark networks, one taken from the DREAM3 Challenges (Marbach et al., 2010; 2009b; Prill et al., 2010) and the other from the DREAM4 Challenges (Marbach et al., 2009a), catalogued in the GNW (Schaffter et al., 2011) database. First, we have done investigations on the former, which has 11 interactions. We have generated four datasets for this network, using GNW (Schaffter et al., 2011) to study the effect of multiple datasets on the network prediction results.

We have presented the results for each of the datasets in [Table 11](#), and the corresponding network structures in [Fig. 4](#). The results show the reduction in the number of FPs for each of the

Table 13

Experimental results of *all possible combinations of models/techniques* for the DREAM3 Challenge network for each individual dataset. (1) PSO, (2) BAPSO, (3) GWPSO, and (4) ABC.

Method Combinations	TP	FP	S_n	S_p	ACC	F-Score	Method Combinations	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 01							Dataset 02					
(1)+(2)	2	16	0.18	0.82	0.75	0.14	(1)+(2)	1	12	0.09	0.87	0.78	0.08
(1)+(3)	2	17	0.18	0.81	0.74	0.13	(1)+(3)	1	12	0.09	0.87	0.78	0.08
(1)+(4)	2	6	0.18	0.93	0.85	0.21	(1)+(4)	1	9	0.09	0.90	0.81	0.10
(2)+(3)	2	16	0.18	0.82	0.75	0.14	(2)+(3)	1	11	0.09	0.88	0.79	0.09
(2)+(4)	2	6	0.18	0.93	0.85	0.21	(2)+(4)	2	9	0.18	0.90	0.82	0.18
(3)+(4)	2	6	0.18	0.93	0.85	0.21	(3)+(4)	1	9	0.09	0.90	0.81	0.10
(1)+(2)+(3)	2	16	0.18	0.82	0.75	0.14	(1)+(2)+(3)	1	11	0.09	0.88	0.79	0.09
(1)+(2)+(4)	2	6	0.18	0.93	0.85	0.21	(1)+(2)+(4)	1	9	0.09	0.90	0.81	0.10
(1)+(3)+(4)	2	6	0.18	0.93	0.85	0.21	(1)+(3)+(4)	1	9	0.09	0.90	0.81	0.10
(2)+(3)+(4)	2	6	0.18	0.93	0.85	0.21	(2)+(3)+(4)	1	9	0.09	0.90	0.81	0.10
(1)+(2)+(3)+(4)	2	6	0.18	0.93	0.85	0.21	(1)+(2)+(3)+(4)	1	9	0.09	0.90	0.81	0.10
Method Combinations	TP	FP	S_n	S_p	ACC	F-Score	Method Combinations	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 03							Dataset 04					
(1)+(2)	3	14	0.27	0.84	0.78	0.21	(1)+(2)	4	13	0.36	0.85	0.80	0.29
(1)+(3)	3	14	0.27	0.84	0.78	0.21	(1)+(3)	4	12	0.36	0.87	0.81	0.30
(1)+(4)	1	10	0.09	0.89	0.80	0.09	(1)+(4)	3	5	0.27	0.94	0.87	0.32
(2)+(3)	3	14	0.27	0.84	0.78	0.21	(2)+(3)	4	12	0.36	0.87	0.81	0.30
(2)+(4)	1	10	0.09	0.89	0.80	0.09	(2)+(4)	3	5	0.27	0.94	0.87	0.32
(3)+(4)	1	10	0.09	0.89	0.80	0.09	(3)+(4)	3	5	0.27	0.94	0.87	0.32
(1)+(2)+(3)	3	14	0.27	0.84	0.78	0.21	(1)+(2)+(3)	4	12	0.36	0.87	0.81	0.30
(1)+(2)+(4)	1	10	0.09	0.89	0.80	0.09	(1)+(2)+(4)	3	5	0.27	0.94	0.87	0.32
(1)+(3)+(4)	1	10	0.09	0.89	0.80	0.09	(1)+(3)+(4)	3	5	0.27	0.94	0.87	0.32
(2)+(3)+(4)	1	10	0.09	0.89	0.80	0.09	(2)+(3)+(4)	3	5	0.27	0.94	0.87	0.32
(1)+(2)+(3)+(4)	1	10	0.09	0.89	0.80	0.09	(1)+(2)+(3)+(4)	3	5	0.27	0.94	0.87	0.32

Table 14

Experimental results of *all possible combinations of models/techniques* applied upon the *dataset ensemble* approach for the DREAM3 Challenge network for each individual dataset. (1) PSO, (2) BAPSO, (3) GWPSO, and (4) ABC.

All Datasets Combined													
Method Combinations	$\alpha = 0.80$						Method Combinations	$\alpha = 0.20$					
	TP	FP	S_n	S_p	ACC	F-Score		TP	FP	S_n	S_p	ACC	F-Score
(1)+(2)	1	0	0.09	1.00	0.90	0.17	(1)+(2)	6	47	0.55	0.47	0.48	0.19
(1)+(3)	1	0	0.09	1.00	0.90	0.17	(1)+(3)	6	46	0.55	0.48	0.49	0.19
(1)+(4)	1	0	0.09	1.00	0.90	0.17	(1)+(4)	5	38	0.45	0.57	0.56	0.19
(2)+(3)	1	0	0.09	1.00	0.90	0.17	(2)+(3)	6	46	0.55	0.48	0.49	0.19
(2)+(4)	1	0	0.09	1.00	0.90	0.17	(2)+(4)	5	38	0.45	0.57	0.56	0.19
(3)+(4)	1	0	0.09	1.00	0.90	0.17	(3)+(4)	5	37	0.45	0.58	0.57	0.19
(1)+(2)+(3)	1	0	0.09	1.00	0.90	0.17	(1)+(2)+(3)	6	46	0.55	0.48	0.49	0.19
(1)+(2)+(4)	1	0	0.09	1.00	0.90	0.17	(1)+(2)+(4)	5	38	0.45	0.57	0.56	0.19
(1)+(3)+(4)	1	0	0.09	1.00	0.90	0.17	(1)+(3)+(4)	5	37	0.45	0.58	0.57	0.19
(2)+(3)+(4)	1	0	0.09	1.00	0.90	0.17	(2)+(3)+(4)	5	37	0.45	0.58	0.57	0.19
(1)+(2)+(3)+(4)	1	0	0.09	1.00	0.90	0.17	(1)+(2)+(3)+(4)	5	37	0.45	0.58	0.57	0.19

Table 15

Experimental results of the *proposed methodology of model/technique combination* for the DREAM4 Challenge network for $\alpha = 0.8$.

Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 01							Dataset 02					
PSO (1)	5	12	0.31	0.86	0.77	0.30	PSO (1)	4	13	0.25	0.85	0.75	0.24
BAPSO (2)	5	13	0.31	0.85	0.76	0.29	BAPSO (2)	4	14	0.25	0.83	0.74	0.24
GWPSO (3)	5	13	0.31	0.85	0.76	0.29	GWPSO (3)	4	14	0.25	0.83	0.74	0.24
ABC (4)	3	9	0.19	0.89	0.78	0.21	ABC (4)	4	10	0.25	0.88	0.78	0.27
(1)+(2)+(3)+(4)	3	9	0.19	0.89	0.78	0.21	(1)+(2)+(3)+(4)	3	9	0.19	0.89	0.78	0.21
Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 03							Dataset 04					
PSO (1)	4	16	0.25	0.81	0.72	0.22	PSO (1)	6	10	0.38	0.88	0.80	0.38
BAPSO (2)	4	16	0.25	0.81	0.72	0.22	BAPSO (2)	5	11	0.31	0.87	0.78	0.31
GWPSO (3)	3	15	0.19	0.82	0.72	0.18	GWPSO (3)	6	10	0.38	0.88	0.80	0.38
ABC (4)	3	8	0.19	0.90	0.79	0.22	ABC (4)	3	7	0.19	0.92	0.80	0.23
(1)+(2)+(3)+(4)	2	7	0.13	0.92	0.79	0.16	(1)+(2)+(3)+(4)	2	6	0.13	0.93	0.80	0.17

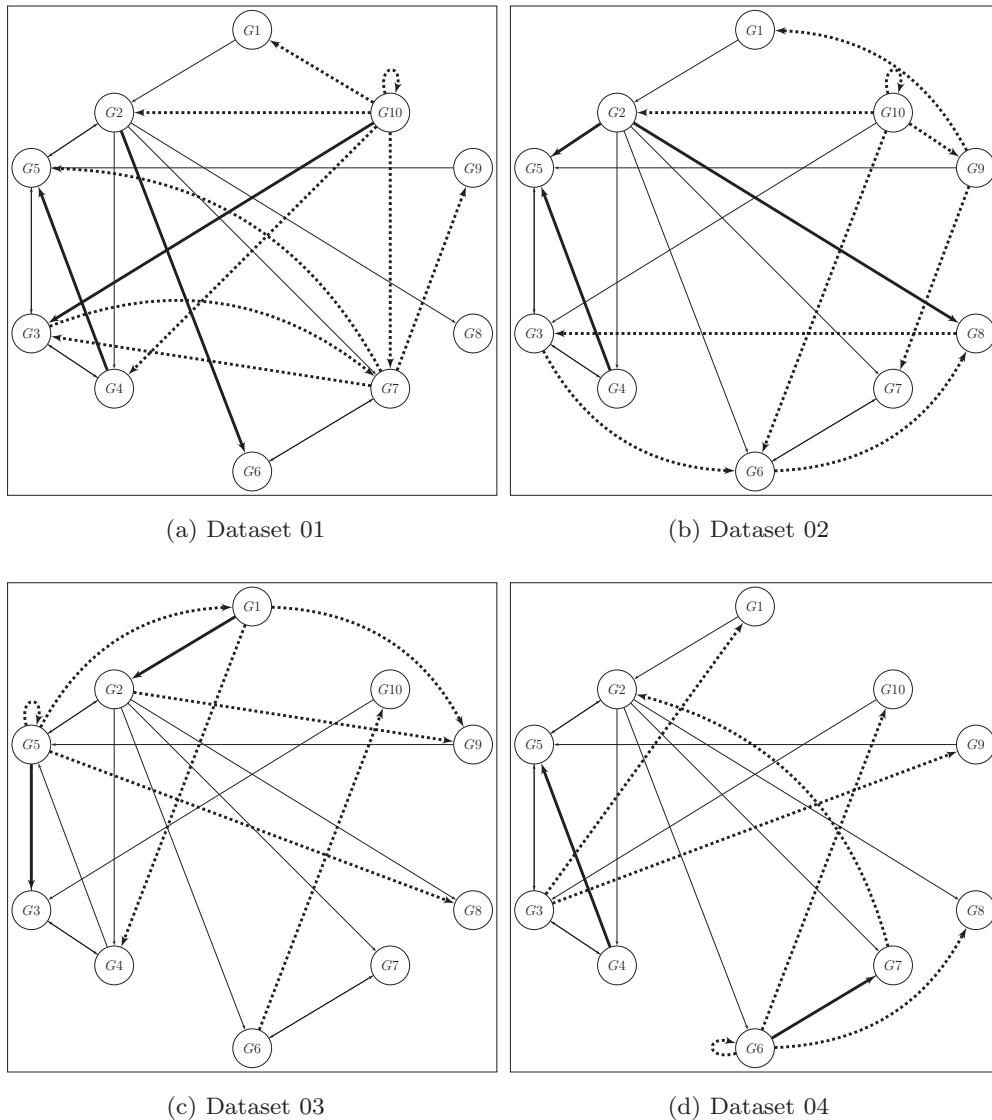


Fig. 5. The structure of 10-gene DREAM4 Challenge network. The thick edges represent those regulations that have been predicted correctly i.e. TPs. The thin edges represent those regulations that could not be predicted, i.e. FNs. The dashed edges represent the spurious relations that have been predicted by our model, i.e. FPs.

datasets. It can be clearly observed that the *specificity* and *accuracy* increases for most of the datasets.

Combining the four datasets, we have obtained the results as shown in Table 12. It can be seen here again that the *dataset ensemble* approach leads to further reduction in the number of TPs which is unsatisfactory. Thus, we have to lower the threshold value α . For the less strict threshold value $\alpha = 0.2$, the proposed methodology can reduce the number of FPs from a maximum of 47 to 37, thus increasing the *specificity* from a minimum of 0.47 to 0.58, an increase of 23.4%, and the *accuracy* from a minimum of 0.48 to 0.57, an increase of 18.75%.

Finally, the results for all possible combinations of the techniques for each dataset has been given separately in Table 13, and for the *dataset ensemble* approach in Table 14.

4.4. 10-gene DREAM4 Challenge network

The second *in silico* gold standard network (a DREAM4 (Marbach et al., 2009a) challenge network) also has 10 genes and 16 interactions. We have generated four datasets in this case also. We have presented the results for each of the datasets in Table 15, and the corresponding network structures in Fig. 5. The results

given in Table 15 clearly show the reduction in the number of FPs for each of the datasets. It can be clearly observed that the *specificity* increases for a majority of the datasets.

We have obtained the results as shown in Table 16 by combining all four datasets. As we have seen from the results presented so far, the combination of multiple datasets does not produce satisfactory results in the case of the current GRN also w.r.t. the number of TPs. We have to lower the threshold to $\alpha = 0.2$, which increases the number of TPs and FPs, both, for the inferred network. Our proposed methodology can still reduce this enhanced number of FPs. The reduction is from a maximum of 45 to 33. Thus, the *specificity* improves from a minimum of 0.46 to 0.61, an improvement of 32.6%. Also, the *accuracy* increases from a minimum of 0.51 to 0.61, an improvement of 19.6%.

Finally, the results for all possible combinations of the techniques for each dataset has been given separately in Table 17, and for the combination of multiple datasets in Table 18.

4.5. 15-gene network extracted from GNW

Next, we have experimented our proposed methodology on the two *in silico* datasets. These datasets have been extracted

Table 16

Experimental results for the *dataset ensemble* approach, and the proposed methodology of model/technique combination applied on it for the DREAM4 Challenge network.

All Datasets Combined													
Methods	$\alpha = 0.80$						Methods	$\alpha = 0.20$					
	TP	FP	S_n	S_p	ACC	F-Score		TP	FP	S_n	S_p	ACC	F-Score
PSO (1)	0	0	0.00	1.00	0.84	0.00	PSO (1)	13	44	0.81	0.48	0.53	0.36
BAPSO (2)	0	0	0.00	1.00	0.84	0.00	BAPSO (2)	13	44	0.81	0.48	0.53	0.36
GWPSO (3)	0	0	0.00	1.00	0.84	0.00	GWPSO (3)	12	45	0.75	0.46	0.51	0.33
ABC (4)	0	0	0.00	1.00	0.84	0.00	ABC (4)	10	39	0.63	0.54	0.55	0.31
(1)+(2)+(3)+(4)	0	0	0.00	1.00	0.84	0.00	(1)+(2)+(3)+(4)	10	33	0.63	0.61	0.61	0.34

Table 17

Experimental results of all possible combinations of models/techniques for the DREAM4 Challenge network for each individual dataset. (1) PSO, (2) BAPSO, (3) GWPSO, and (4) ABC.

Method Combinations	TP	FP	S_n	S_p	ACC	F-Score	Method Combinations	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 01							Dataset 02					
(1)+(2)	5	12	0.31	0.86	0.77	0.30	(1)+(2)	4	13	0.25	0.85	0.75	0.24
(1)+(3)	5	12	0.31	0.86	0.77	0.30	(1)+(3)	4	13	0.25	0.85	0.75	0.24
(1)+(4)	3	9	0.19	0.89	0.78	0.21	(1)+(4)	3	9	0.19	0.89	0.78	0.21
(2)+(3)	5	12	0.31	0.86	0.77	0.30	(2)+(3)	4	13	0.25	0.85	0.75	0.24
(2)+(4)	3	9	0.19	0.89	0.78	0.21	(2)+(4)	3	9	0.19	0.89	0.78	0.21
(3)+(4)	3	9	0.19	0.89	0.78	0.21	(3)+(4)	3	9	0.19	0.89	0.78	0.21
(1)+(2)+(3)	5	12	0.31	0.86	0.77	0.30	(1)+(2)+(3)	4	13	0.25	0.85	0.75	0.24
(1)+(2)+(4)	3	9	0.19	0.89	0.78	0.21	(1)+(2)+(4)	3	9	0.19	0.89	0.78	0.21
(1)+(3)+(4)	3	9	0.19	0.89	0.78	0.21	(1)+(3)+(4)	3	9	0.19	0.89	0.78	0.21
(2)+(3)+(4)	3	9	0.19	0.89	0.78	0.21	(2)+(3)+(4)	3	9	0.19	0.89	0.78	0.21
(1)+(2)+(3)+(4)	3	9	0.19	0.89	0.78	0.21	(1)+(2)+(3)+(4)	3	9	0.19	0.89	0.78	0.21
Method Combinations	TP	FP	S_n	S_p	ACC	F-Score	Method Combinations	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 03							Dataset 04					
(1)+(2)	4	16	0.25	0.81	0.72	0.22	(1)+(2)	5	10	0.31	0.88	0.79	0.32
(1)+(3)	3	15	0.19	0.82	0.72	0.18	(1)+(3)	5	8	0.31	0.90	0.81	0.34
(1)+(4)	2	7	0.13	0.92	0.79	0.16	(1)+(4)	2	7	0.13	0.92	0.79	0.16
(2)+(3)	3	15	0.19	0.82	0.72	0.18	(2)+(3)	5	9	0.31	0.89	0.80	0.33
(2)+(4)	2	7	0.13	0.92	0.79	0.16	(2)+(4)	2	7	0.13	0.92	0.79	0.16
(3)+(4)	2	7	0.13	0.92	0.79	0.16	(3)+(4)	3	6	0.19	0.93	0.81	0.24
(1)+(2)+(3)	3	15	0.19	0.82	0.72	0.18	(1)+(2)+(3)	5	8	0.31	0.90	0.81	0.34
(1)+(2)+(4)	2	7	0.13	0.92	0.79	0.16	(1)+(2)+(4)	2	7	0.13	0.92	0.79	0.16
(1)+(3)+(4)	2	7	0.13	0.92	0.79	0.16	(1)+(3)+(4)	2	6	0.13	0.93	0.80	0.17
(2)+(3)+(4)	2	7	0.13	0.92	0.79	0.16	(2)+(3)+(4)	2	6	0.13	0.93	0.80	0.17
(1)+(2)+(3)+(4)	2	7	0.13	0.92	0.79	0.16	(1)+(2)+(3)+(4)	2	6	0.13	0.93	0.80	0.17

Table 18

Experimental results of all possible combinations of models/techniques applied upon the *dataset ensemble* approach for the DREAM4 Challenge network for each individual dataset. (1) PSO, (2) BAPSO, (3) GWPSO, and (4) ABC.

All Datasets Combined													
Method Combinations	$\alpha = 0.80$						Method Combinations	$\alpha = 0.20$					
	TP	FP	S_n	S_p	ACC	F-Score		TP	FP	S_n	S_p	ACC	F-Score
(1)+(2)	0	0	0.00	1.00	0.84	0.00	(1)+(2)	13	44	0.81	0.48	0.53	0.36
(1)+(3)	0	0	0.00	1.00	0.84	0.00	(1)+(3)	12	42	0.75	0.50	0.54	0.34
(1)+(4)	0	0	0.00	1.00	0.84	0.00	(1)+(4)	10	34	0.63	0.60	0.60	0.33
(2)+(3)	0	0	0.00	1.00	0.84	0.00	(2)+(3)	12	42	0.75	0.50	0.54	0.34
(2)+(4)	0	0	0.00	1.00	0.84	0.00	(2)+(4)	10	34	0.63	0.60	0.60	0.33
(3)+(4)	0	0	0.00	1.00	0.84	0.00	(3)+(4)	10	33	0.63	0.61	0.61	0.34
(1)+(2)+(3)	0	0	0.00	1.00	0.84	0.00	(1)+(2)+(3)	12	42	0.75	0.50	0.54	0.34
(1)+(2)+(4)	0	0	0.00	1.00	0.84	0.00	(1)+(2)+(4)	10	34	0.63	0.60	0.60	0.33
(1)+(3)+(4)	0	0	0.00	1.00	0.84	0.00	(1)+(3)+(4)	10	33	0.63	0.61	0.61	0.34
(2)+(3)+(4)	0	0	0.00	1.00	0.84	0.00	(2)+(3)+(4)	10	33	0.63	0.61	0.61	0.34
(1)+(2)+(3)+(4)	0	0	0.00	1.00	0.84	0.00	(1)+(2)+(3)+(4)	10	33	0.63	0.61	0.61	0.34

Table 19

Experimental results of the proposed methodology of model/technique combination for the 15-gene network extracted from GNW for $\alpha = 0.8$.

Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 01							Dataset 02					
PSO (1)	4	20	0.21	0.90	0.84	0.19	PSO (1)	1	21	0.05	0.90	0.83	0.05
BAPSO (2)	4	21	0.21	0.90	0.84	0.18	BAPSO (2)	1	22	0.05	0.89	0.82	0.05
GWPSO (3)	2	17	0.11	0.92	0.85	0.11	GWPSO (3)	1	16	0.05	0.92	0.85	0.06
ABC (4)	2	14	0.11	0.93	0.86	0.11	ABC (4)	1	19	0.05	0.91	0.84	0.05
(1)+(2)+(3)+(4)	2	9	0.11	0.96	0.88	0.13	(1)+(2)+(3)+(4)	0	9	0.00	0.96	0.88	0.00
Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 03							Dataset 04					
PSO (1)	2	21	0.11	0.90	0.83	0.10	PSO (1)	1	23	0.05	0.89	0.82	0.05
BAPSO (2)	3	24	0.16	0.88	0.82	0.13	BAPSO (2)	1	23	0.05	0.89	0.82	0.05
GWPSO (3)	1	20	0.05	0.90	0.83	0.05	GWPSO (3)	2	19	0.11	0.91	0.84	0.10
ABC (4)	1	21	0.05	0.90	0.83	0.05	ABC (4)	1	17	0.05	0.92	0.84	0.05
(1)+(2)+(3)+(4)	0	15	0.00	0.93	0.85	0.00	(1)+(2)+(3)+(4)	1	12	0.05	0.94	0.87	0.06

Table 20

Experimental results for the dataset ensemble approach, and the proposed methodology of model/technique combination applied on it for the 15-gene network extracted from GNW.

All Datasets Combined													
Methods	$\alpha = 0.80$						Methods	$\alpha = 0.20$					
	TP	FP	S_n	S_p	ACC	F-Score		TP	FP	S_n	S_p	ACC	F-Score
PSO (1)	0	0	0.00	1.00	0.92	0.00	PSO (1)	8	79	0.42	0.62	0.60	0.15
BAPSO (2)	0	0	0.00	1.00	0.92	0.00	BAPSO (2)	9	78	0.47	0.62	0.61	0.17
GWPSO (3)	0	0	0.00	1.00	0.92	0.00	GWPSO (3)	6	70	0.32	0.66	0.63	0.13
ABC (4)	0	2	0.00	0.99	0.91	0.00	ABC (4)	4	63	0.21	0.69	0.65	0.09
(1)+(2)+(3)+(4)	0	0	0.00	1.00	0.92	0.00	(1)+(2)+(3)+(4)	3	55	0.16	0.73	0.68	0.08

Table 21

Experimental results of all possible combinations of models/techniques for the 15-gene network extracted from GNW for each individual dataset. (1) PSO, (2) BAPSO, (3) GWPSO, and (4) ABC.

Method Combinations	TP	FP	S_n	S_p	ACC	F-Score	Method Combinations	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 01							Dataset 02					
(1)+(2)	4	18	0.21	0.91	0.85	0.20	(1)+(2)	1	19	0.05	0.91	0.84	0.05
(1)+(3)	2	17	0.11	0.92	0.85	0.11	(1)+(3)	0	16	0.00	0.92	0.84	0.00
(1)+(4)	2	10	0.11	0.95	0.88	0.13	(1)+(4)	0	11	0.00	0.95	0.87	0.00
(2)+(3)	2	17	0.11	0.92	0.85	0.11	(2)+(3)	0	15	0.00	0.93	0.85	0.00
(2)+(4)	2	11	0.11	0.95	0.88	0.13	(2)+(4)	0	12	0.00	0.94	0.86	0.00
(3)+(4)	2	9	0.11	0.96	0.88	0.13	(3)+(4)	0	10	0.00	0.95	0.87	0.00
(1)+(2)+(3)	2	17	0.11	0.92	0.85	0.11	(1)+(2)+(3)	0	15	0.00	0.93	0.85	0.00
(1)+(2)+(4)	2	9	0.11	0.96	0.88	0.13	(1)+(2)+(4)	0	10	0.00	0.95	0.87	0.00
(1)+(3)+(4)	2	9	0.11	0.96	0.88	0.13	(1)+(3)+(4)	0	10	0.00	0.95	0.87	0.00
(2)+(3)+(4)	2	9	0.11	0.96	0.88	0.13	(2)+(3)+(4)	0	9	0.00	0.96	0.88	0.00
(1)+(2)+(3)+(4)	2	9	0.11	0.96	0.88	0.13	(1)+(2)+(3)+(4)	0	9	0.00	0.96	0.88	0.00
Method Combinations	TP	FP	S_n	S_p	ACC	F-Score	Method Combinations	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 03							Dataset 04					
(1)+(2)	2	19	0.11	0.91	0.84	0.10	(1)+(2)	1	19	0.05	0.91	0.84	0.05
(1)+(3)	1	18	0.05	0.91	0.84	0.05	(1)+(3)	1	18	0.05	0.91	0.84	0.05
(1)+(4)	0	15	0.00	0.93	0.85	0.00	(1)+(4)	1	13	0.05	0.94	0.86	0.06
(2)+(3)	1	18	0.05	0.91	0.84	0.05	(2)+(3)	1	18	0.05	0.91	0.84	0.05
(2)+(4)	1	19	0.05	0.91	0.84	0.05	(2)+(4)	1	14	0.05	0.93	0.86	0.06
(3)+(4)	0	16	0.00	0.92	0.84	0.00	(3)+(4)	1	12	0.05	0.94	0.87	0.06
(1)+(2)+(3)	1	18	0.05	0.91	0.84	0.05	(1)+(2)+(3)	1	17	0.05	0.92	0.84	0.05
(1)+(2)+(4)	0	15	0.00	0.93	0.85	0.00	(1)+(2)+(4)	1	13	0.05	0.94	0.86	0.06
(1)+(3)+(4)	0	15	0.00	0.93	0.85	0.00	(1)+(3)+(4)	1	12	0.05	0.94	0.87	0.06
(2)+(3)+(4)	0	15	0.00	0.93	0.85	0.00	(2)+(3)+(4)	1	12	0.05	0.94	0.87	0.06
(1)+(2)+(3)+(4)	0	15	0.00	0.93	0.85	0.00	(1)+(2)+(3)+(4)	1	12	0.05	0.94	0.87	0.06

Table 22

Experimental results of all possible combinations of models/techniques applied upon the dataset ensemble approach for the 15-gene network extracted from GNW for each individual dataset. (1) PSO, (2) BAPSO, (3) GWPSO, and (4) ABC.

Method Combinations	All Datasets Combined												
	$\alpha = 0.80$			$\alpha = 0.20$									
	TP	FP	S_n	S_p	ACC	F-Score	TP	FP	S_n	S_p	ACC	F-Score	
(1)+(2)	0	0	0.00	1.00	0.92	0.00	(1)+(2)	8	74	0.42	0.64	0.62	0.16
(1)+(3)	0	0	0.00	1.00	0.92	0.00	(1)+(3)	5	68	0.26	0.67	0.64	0.11
(1)+(4)	0	0	0.00	1.00	0.92	0.00	(1)+(4)	3	56	0.16	0.73	0.68	0.08
(2)+(3)	0	0	0.00	1.00	0.92	0.00	(2)+(3)	6	68	0.32	0.67	0.64	0.13
(2)+(4)	0	0	0.00	1.00	0.92	0.00	(2)+(4)	4	58	0.21	0.72	0.68	0.10
(3)+(4)	0	0	0.00	1.00	0.92	0.00	(3)+(4)	4	56	0.21	0.73	0.68	0.10
(1)+(2)+(3)	0	0	0.00	1.00	0.92	0.00	(1)+(2)+(3)	5	68	0.26	0.67	0.64	0.11
(1)+(2)+(4)	0	0	0.00	1.00	0.92	0.00	(1)+(2)+(4)	3	56	0.16	0.73	0.68	0.08
(1)+(3)+(4)	0	0	0.00	1.00	0.92	0.00	(1)+(3)+(4)	3	55	0.16	0.73	0.68	0.08
(2)+(3)+(4)	0	0	0.00	1.00	0.92	0.00	(2)+(3)+(4)	4	55	0.21	0.73	0.69	0.10
(1)+(2)+(3)+(4)	0	0	0.00	1.00	0.92	0.00	(1)+(2)+(3)+(4)	3	55	0.16	0.73	0.68	0.08

Table 23

Experimental results of the proposed methodology of model/technique combination for the 20-gene network extracted from GNW for $\alpha = 0.8$.

Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
								Dataset 01					
PSO (1)	4	26	0.17	0.93	0.89	0.15	PSO (1)	7	24	0.29	0.94	0.90	0.25
BAPSO (2)	4	30	0.17	0.92	0.88	0.14	BAPSO (2)	7	27	0.29	0.93	0.89	0.24
GWPSO (3)	4	25	0.17	0.93	0.89	0.15	GWPSO (3)	7	24	0.29	0.94	0.90	0.25
ABC (4)	3	19	0.13	0.95	0.90	0.13	ABC (4)	6	16	0.25	0.96	0.92	0.26
(1)+(2)+(3)+(4)	3	17	0.13	0.95	0.91	0.14	(1)+(2)+(3)+(4)	6	15	0.25	0.96	0.92	0.27
Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
								Dataset 03					
PSO (1)	4	29	0.17	0.92	0.88	0.14	PSO (1)	5	26	0.21	0.93	0.89	0.18
BAPSO (2)	4	30	0.17	0.92	0.88	0.14	BAPSO (2)	6	30	0.25	0.92	0.88	0.20
GWPSO (3)	4	28	0.17	0.93	0.88	0.14	GWPSO (3)	4	27	0.17	0.93	0.88	0.15
ABC (4)	4	21	0.17	0.94	0.90	0.16	ABC (4)	5	16	0.21	0.96	0.91	0.22
(1)+(2)+(3)+(4)	3	15	0.13	0.96	0.91	0.14	(1)+(2)+(3)+(4)	3	13	0.13	0.97	0.92	0.15

Table 24

Experimental results for the dataset ensemble approach, and the proposed methodology of model/technique combination applied on it for the 20-gene network extracted from GNW.

Methods	All Datasets Combined												
	$\alpha = 0.80$			$\alpha = 0.20$									
Methods	TP	FP	S_n	S_p	ACC	F-Score	Methods	TP	FP	S_n	S_p	ACC	F-Score
PSO (1)	2	2	0.08	0.99	0.94	0.14	PSO (1)	11	96	0.46	0.74	0.73	0.17
BAPSO (2)	2	2	0.08	0.99	0.94	0.14	BAPSO (2)	11	102	0.46	0.73	0.71	0.16
GWPSO (3)	2	2	0.08	0.99	0.94	0.14	GWPSO (3)	11	93	0.46	0.75	0.74	0.17
ABC (4)	2	2	0.08	0.99	0.94	0.14	ABC (4)	11	75	0.46	0.80	0.78	0.20
(1)+(2)+(3)+(4)	2	2	0.08	0.99	0.94	0.14	(1)+(2)+(3)+(4)	10	62	0.42	0.84	0.81	0.21

from GNW (Schaffter et al., 2011) to investigate the performance of our proposed methodology on moderate-sized networks. The network dynamics in both the cases has been generated by GNW (Schaffter et al., 2011) using DREAM4 (Marbach et al., 2009a) settings. We have generated four datasets for each.

The first one is a 15-gene GRN that has 19 interactions. The obtained results have been depicted in Tables 19–22. In Table 19, we have presented the results for all the datasets, individually. The significant reduction in the number of FPs achieved by our proposed methodology can be clearly seen from this table, for each of the datasets investigated. The corresponding network structures have been given in Fig. 6. The results obtained by combining all four datasets have been presented in Table 20.

It can be seen from Table 20 that when all the datasets have been combined, the number of TPs along with FPs inferred by the individual techniques vastly reduce, even to 0. We have seen this phenomenon in almost all the previous experiments. Thus, the proposed techniques gets no information at all. In order to fetch more information for our proposed technique, we need to reduce the threshold value, α .

With the reduced threshold of $\alpha = 0.2$, our proposed technique can reduce the number of FPs significantly, which is our main objective. The FPs reduce from a maximum of 79 to 55. Consequently, the specificity improves from 0.62 to 0.79, an increase of 27.4%. On the other hand, the accuracy increases from a minimum of 0.60 to 0.68, an improvement of 13.3%. It is interesting to note that the

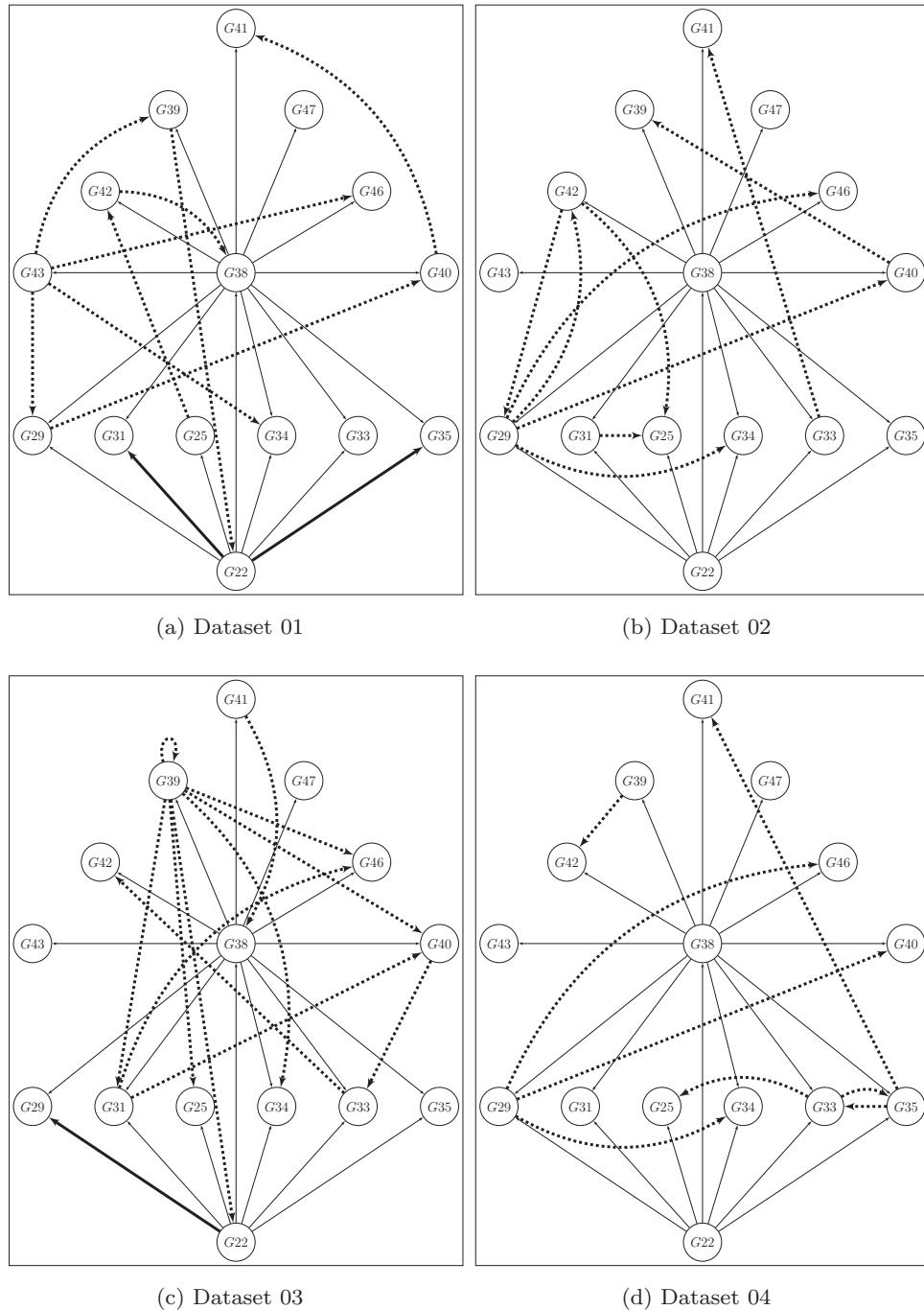


Fig. 6. The structure of the 15-gene network extracted from GNW. The thick edges represent those regulations that have been predicted correctly i.e. TPs. The thin edges represent those regulations that could not be predicted, i.e. FNs. The dashed edges represent the spurious relations that have been predicted by our model, i.e. FPs.

number of TPs increases significantly when threshold is reduced from $\alpha = 0.8$ to $\alpha = 0.2$.

Finally, results for all possible combinations of the metaheuristic techniques have been given for each dataset, separately, in Table 21, and for all the datasets combined in Table 22.

4.6. 20-gene network extracted from GNW

Finally, we have experimented upon a 20-gene GRN with 24 interactions. The network dynamics has been generated by GNW (Schaffter et al., 2011) using DREAM4 (Marbach et al., 2009a) settings. We have generated four datasets. The obtained results have

been depicted in Tables 23–26. In Table 23, we have presented the results for all the datasets, individually. The significant reduction in the number of FPs achieved by our proposed methodology can be clearly seen from this table, for each of the datasets investigated. The corresponding network structures have been given in Figure 7. The results obtained by combining all four datasets have been presented in Table 24.

Finally, in this experiment also, we find that combining all the datasets reduces the number of TPs along with FPs, drastically. For this reason, we have to generate the individual networks using a lower threshold of $\alpha = 0.2$. However, it can be seen from Table 24 that the FP reduction capacity of the proposed method-

Table 25

Experimental results of *all possible combinations of models/techniques* for the 20-gene network extracted from GNW for each individual dataset. (1) PSO, (2) BAPSO, (3) GWPSO, and (4) ABC.

Method Combinations	TP	FP	S_n	S_p	ACC	F-Score	Method Combinations	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 01							Dataset 02					
(1)+(2)	4	24	0.17	0.94	0.89	0.15	(1)+(2)	7	24	0.29	0.94	0.90	0.25
(1)+(3)	4	25	0.17	0.93	0.89	0.15	(1)+(3)	7	21	0.29	0.94	0.91	0.27
(1)+(4)	3	17	0.13	0.95	0.91	0.14	(1)+(4)	6	15	0.25	0.96	0.92	0.27
(2)+(3)	4	23	0.17	0.94	0.89	0.16	(2)+(3)	7	22	0.29	0.94	0.90	0.26
(2)+(4)	3	18	0.13	0.95	0.90	0.13	(2)+(4)	6	15	0.25	0.96	0.92	0.27
(3)+(4)	3	17	0.13	0.95	0.91	0.14	(3)+(4)	6	15	0.25	0.96	0.92	0.27
(1)+(2)+(3)	4	23	0.17	0.94	0.89	0.16	(1)+(2)+(3)	7	21	0.29	0.94	0.91	0.27
(1)+(2)+(4)	3	17	0.13	0.95	0.91	0.14	(1)+(2)+(4)	6	15	0.25	0.96	0.92	0.27
(1)+(3)+(4)	3	17	0.13	0.95	0.91	0.14	(1)+(3)+(4)	6	15	0.25	0.96	0.92	0.27
(2)+(3)+(4)	3	17	0.13	0.95	0.91	0.14	(2)+(3)+(4)	6	15	0.25	0.96	0.92	0.27
(1)+(2)+(3)+(4)	3	17	0.13	0.95	0.91	0.14	(1)+(2)+(3)+(4)	6	15	0.25	0.96	0.92	0.27
Method Combinations	TP	FP	S_n	S_p	ACC	F-Score	Method Combinations	TP	FP	S_n	S_p	ACC	F-Score
	Dataset 03							Dataset 04					
(1)+(2)	4	26	0.17	0.93	0.89	0.15	(1)+(2)	4	26	0.17	0.93	0.89	0.15
(1)+(3)	4	26	0.17	0.93	0.89	0.15	(1)+(3)	3	25	0.13	0.93	0.89	0.12
(1)+(4)	3	17	0.13	0.95	0.91	0.14	(1)+(4)	4	13	0.17	0.97	0.92	0.20
(2)+(3)	4	27	0.17	0.93	0.88	0.15	(2)+(3)	4	26	0.17	0.93	0.89	0.15
(2)+(4)	3	18	0.13	0.95	0.90	0.13	(2)+(4)	5	15	0.21	0.96	0.92	0.23
(3)+(4)	3	17	0.13	0.95	0.91	0.14	(3)+(4)	3	14	0.13	0.96	0.91	0.15
(1)+(2)+(3)	4	25	0.17	0.93	0.89	0.15	(1)+(2)+(3)	3	25	0.13	0.93	0.89	0.12
(1)+(2)+(4)	3	15	0.13	0.96	0.91	0.14	(1)+(2)+(4)	4	13	0.17	0.97	0.92	0.20
(1)+(3)+(4)	3	15	0.13	0.96	0.91	0.14	(1)+(3)+(4)	3	13	0.13	0.97	0.92	0.15
(2)+(3)+(4)	3	17	0.13	0.95	0.91	0.14	(2)+(3)+(4)	3	14	0.13	0.96	0.91	0.15
(1)+(2)+(3)+(4)	3	15	0.13	0.96	0.91	0.14	(1)+(2)+(3)+(4)	3	13	0.13	0.97	0.92	0.15

Table 26

Experimental results of *all possible combinations of models/techniques* applied upon the *dataset ensemble* approach for the 20-gene network extracted from GNW for each individual dataset. (1) PSO, (2) BAPSO, (3) GWPSO, and (4) ABC.

Method Combinations	All Datasets Combined						Method Combinations	All Datasets Combined					
	$\alpha = 0.80$							$\alpha = 0.20$					
Method Combinations	TP	FP	S_n	S_p	ACC	F-Score	Method Combinations	TP	FP	S_n	S_p	ACC	F-Score
(1)+(2)	2	2	0.08	0.99	0.94	0.14	(1)+(2)	11	88	0.46	0.77	0.75	0.18
(1)+(3)	2	2	0.08	0.99	0.94	0.14	(1)+(3)	11	85	0.46	0.77	0.76	0.18
(1)+(4)	2	2	0.08	0.99	0.94	0.14	(1)+(4)	10	64	0.42	0.83	0.81	0.20
(2)+(3)	2	2	0.08	0.99	0.94	0.14	(2)+(3)	11	88	0.46	0.77	0.75	0.18
(2)+(4)	2	2	0.08	0.99	0.94	0.14	(2)+(4)	10	70	0.42	0.81	0.79	0.19
(3)+(4)	2	2	0.08	0.99	0.94	0.14	(3)+(4)	10	66	0.42	0.82	0.80	0.20
(1)+(2)+(3)	2	2	0.08	0.99	0.94	0.14	(1)+(2)+(3)	11	82	0.46	0.78	0.76	0.19
(1)+(2)+(4)	2	2	0.08	0.99	0.94	0.14	(1)+(2)+(4)	10	63	0.42	0.83	0.81	0.21
(1)+(3)+(4)	2	2	0.08	0.99	0.94	0.14	(1)+(3)+(4)	10	62	0.42	0.84	0.81	0.21
(2)+(3)+(4)	2	2	0.08	0.99	0.94	0.14	(2)+(3)+(4)	10	66	0.42	0.82	0.80	0.20
(1)+(2)+(3)+(4)	2	2	0.08	0.99	0.94	0.14	(1)+(2)+(3)+(4)	10	62	0.42	0.84	0.81	0.21

ology is clearly evident even when using the lower threshold of $\alpha = 0.2$. We have achieved our main objective of reducing the number of FPs successfully in the case of the *dataset ensemble* approach with $\alpha = 0.2$ also. The number of FPs reduce from a maximum of 102 to 62. Consequently, the *specificity* improves from 0.73 to 0.84, an increase of 15.1%. On the other hand, the *accuracy* increases from a minimum of 0.71 to 0.81, an improvement of 14.1%.

Finally, results for all possible combinations of the metaheuristic techniques have been given for each dataset, separately, in Table 25.

4.7. Effect of prior biological information

Recent research endeavours (Chowdhury and Chetty, 2015) have indicated that due to the significantly huge computation required

for the reverse engineering of large-scale GRNs, network modelling formalisms based on prior biological knowledge are needed. Therefore, in this work, we have studied the effect of prior biological knowledge on the proposed false positive reduction technique. It is very encouraging to see that even with 30% of the information known, most of the true positives survive the filtering procedure, and sometimes it is improved also, as evident in our experiments performed herein. However, further reduction in the number of FPs is not achievable using prior knowledge incorporation in our proposed methodology. The results for each of the four *in silico* networks have been shown in Tables 27 and 28, for such a scenario. It can be seen that in addition to the maximum reduction in FPs achieved by our proposed methodology, the number of TPs increases from the computational methods proposed which is a very encouraging outcome from our investigations.

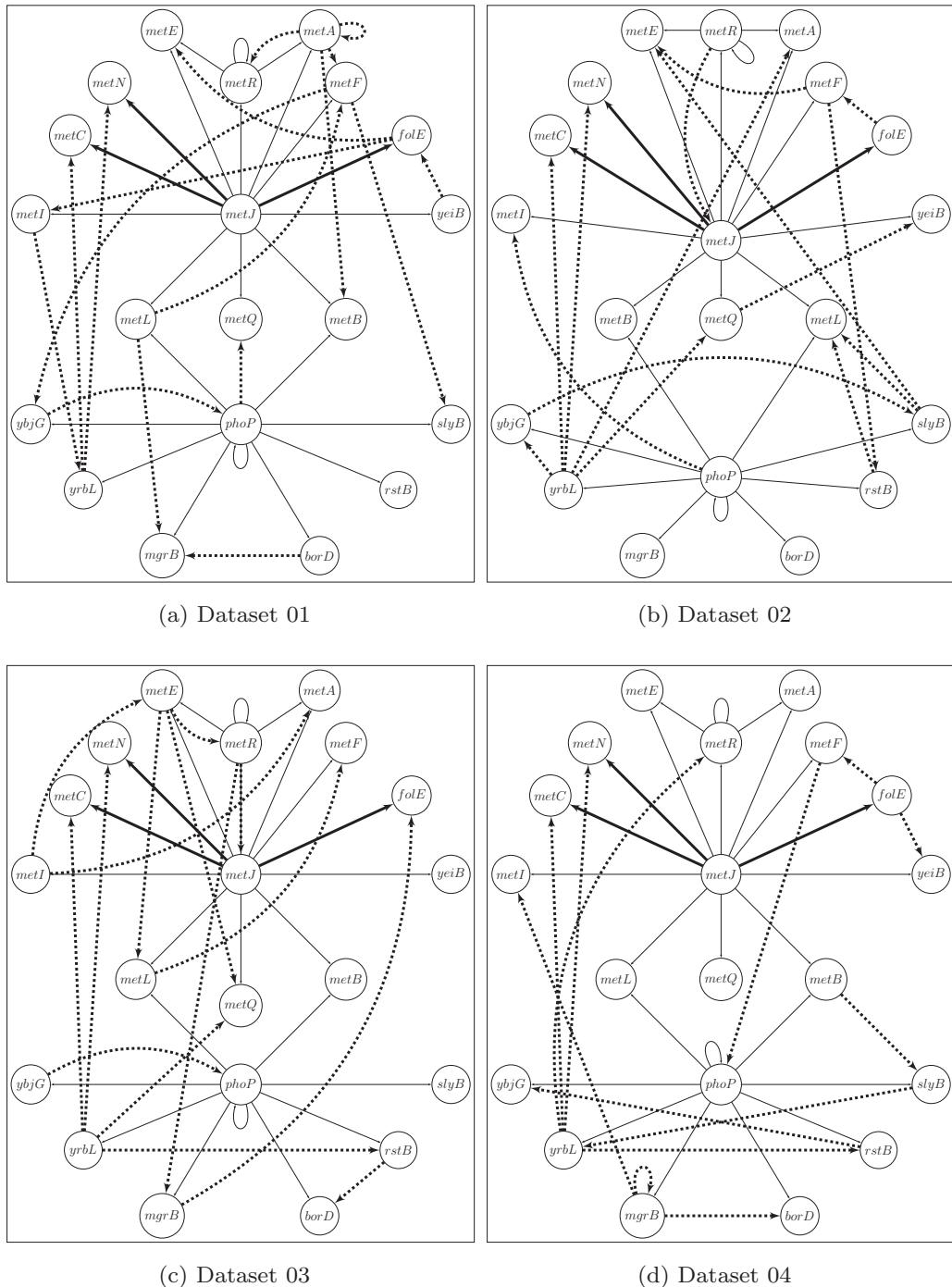


Fig. 7. The structure of the 20-gene network extracted from GNW. The thick edges represent those regulations that have been predicted correctly i.e. TPs. The thin edges represent those regulations that could not be predicted, i.e. FNs. The dashed edges represent the spurious relations that have been predicted by our model, i.e. FPs.

5. Conclusion

A fully evolved computational methodology for the reverse engineering of GRNs from temporal gene expression data is still eluding the research fraternity. There are several techniques in the contemporary literature that have been proposed and developed so far for this sole purpose. The main drawback of such techniques is the prediction of only a few of the actual genetic relationships existing in a network, i.e. only few TPs are inferred. However, along with this they also predict many incorrect genetic interactions, i.e. non-existent relationships or FPs.

In this present research endeavour, we have proposed a methodology to further reduce the number of inferred FPs. Here, we have investigated into the reverse engineering of GRNs from time-series gene expression datasets, based on the RNN formalism with four different swarm intelligence techniques, namely, PSO, BAPSO, GWPPO, and ABC.

In our experiments, we have applied our proposed formalism to six genetic networks of various origins. For each network, we have used four different datasets to further investigate and compare the efficiency of our proposed methodology in the presence of multiple datasets, i.e. a dataset ensemble approach.

Table 27

Comparison of results obtained for the *in silico* benchmark, i.e. DREAM3 and DREAM4, Challenge networks with and without prior biological knowledge available about the networks.

	TP	FP	S_n	S_p	ACC	F-Score	Graph Edges
10-gene DREAM3: Dataset 01							
Without prior biological knowledge	2	6	0.18	0.93	0.85	0.21	8
With prior biological knowledge	2	6	0.18	0.93	0.85	0.21	8
Dataset 02							
Without prior biological knowledge	1	9	0.09	0.90	0.81	0.10	10
With prior biological knowledge	2	9	0.18	0.90	0.82	0.18	11
Dataset 03							
Without prior biological knowledge	1	10	0.09	0.89	0.80	0.09	11
With prior biological knowledge	3	10	0.27	0.89	0.82	0.25	13
Dataset 04							
Without prior biological knowledge	3	5	0.27	0.94	0.87	0.32	8
With prior biological knowledge	4	5	0.36	0.94	0.88	0.40	9
All Datasets Combined with $\alpha = 0.2$							
Without prior biological knowledge	5	37	0.45	0.58	0.57	0.19	42
With prior biological knowledge	6	37	0.55	0.58	0.58	0.22	43
10-gene DREAM4: Dataset 01							
Without prior biological knowledge	3	9	0.19	0.89	0.78	0.21	12
With prior biological knowledge	5	9	0.31	0.89	0.80	0.33	14
Dataset 02							
Without prior biological knowledge	3	9	0.19	0.89	0.78	0.21	12
With prior biological knowledge	4	9	0.25	0.89	0.79	0.28	13
Dataset 03							
Without prior biological knowledge	2	7	0.13	0.92	0.79	0.16	9
With prior biological knowledge	5	7	0.31	0.92	0.82	0.36	12
Dataset 04							
Without prior biological knowledge	2	6	0.13	0.93	0.80	0.17	8
With prior biological knowledge	5	6	0.31	0.93	0.83	0.37	11
All Datasets Combined with $\alpha = 0.2$							
Without prior biological knowledge	10	33	0.63	0.61	0.61	0.34	43
With prior biological knowledge	12	33	0.75	0.61	0.63	0.39	45

proach of sorts. For the individual datasets, inferred networks have been generated for each technique using a strict threshold of plausibility score $\alpha = 0.8$. When using the combination of four datasets, we have had to perform our experimentation using two values of threshold of plausibility score, $\alpha = 0.2$ and $\alpha = 0.8$. The former signifies a lesser filtration thus allowing more information, while the later indicates a stricter filtration with lesser information.

We have experimented in various ways to observe which method reduces the FPs effectively while producing as little disturbance as possible for the predicted TPs. The types of experimentations that we have executed here are:

- (i) combining the results obtained from the RNN formalism using the four swarm intelligence techniques from each dataset;

- (ii) combining the results from the four different datasets for each technique (i.e. the *dataset ensemble* approach);
- (iii) aggregating the results obtained for each individual dataset in all the different possible combination of techniques (i.e. in groups of two, three and four); and finally,
- (iv) aggregating all the results obtained using the dataset ensemble approach for all the different possible combination of techniques for $\alpha = 0.2$ and $\alpha = 0.8$.

The observations from the results obtained are very interesting in nature. First of all, reduction in the number of FPs has been achieved by our proposed methodology to various degrees in almost all of the experiments performed in this work. Secondly, it is quite clear from the presented results that in most of the cases, the proposed methodology is successful in achieving an improvement

Table 28

Comparison of results obtained for the 15-gene and 20-gene networks, extracted from GNW with and without prior biological knowledge available about the networks.

	TP	FP	S_n	S_p	ACC	F-Score	Graph Edges
15-gene: Dataset 01							
Without prior biological knowledge	2	9	0.11	0.96	0.88	0.13	11
With prior biological knowledge	4	9	0.21	0.96	0.89	0.25	13
Dataset 02							
Without prior biological knowledge	0	9	0.00	0.96	0.88	0.00	9
With prior biological knowledge	2	9	0.11	0.96	0.88	0.13	11
Dataset 03							
Without prior biological knowledge	0	15	0.00	0.93	0.85	0.00	15
With prior biological knowledge	2	15	0.11	0.93	0.86	0.11	17
Dataset 04							
Without prior biological knowledge	1	12	0.05	0.94	0.87	0.06	13
With prior biological knowledge	2	12	0.11	0.94	0.87	0.12	14
All Datasets Combined with $\alpha = 0.2$							
Without prior biological knowledge	4	55	0.21	0.73	0.69	0.10	59
With prior biological knowledge	6	55	0.32	0.73	0.70	0.15	61
20-gene: Dataset 01							
Without prior biological knowledge	3	17	0.13	0.95	0.91	0.14	20
With prior biological knowledge	4	17	0.17	0.95	0.91	0.18	21
Dataset 02							
Without prior biological knowledge	6	15	0.25	0.96	0.92	0.27	21
With prior biological knowledge	7	15	0.29	0.96	0.92	0.30	22
Dataset 03							
Without prior biological knowledge	3	15	0.13	0.96	0.91	0.14	18
With prior biological knowledge	4	15	0.17	0.96	0.91	0.19	19
Dataset 04							
Without prior biological knowledge	3	13	0.13	0.97	0.92	0.15	16
With prior biological knowledge	4	13	0.17	0.97	0.92	0.20	17
All Datasets Combined with $\alpha = 0.2$							
Without prior biological knowledge	10	62	0.42	0.84	0.81	0.21	72
With prior biological knowledge	11	62	0.46	0.84	0.81	0.23	73

w.r.t. the quality measures like *specificity* and *accuracy* over several datasets, and also when multiple datasets have been combined.

Furthermore, although our proposed methodology has not been designed to bring about improvements w.r.t. the number of TPs, we have tried to do the same using the dataset ensemble approach and decreasing the value of the plausibility score threshold to $\alpha = 0.2$ from that of $\alpha = 0.8$. We have achieved an improvement w.r.t. to the absolute number of TPs but at the cost of a larger number of FPs compared to the case of individual datasets with $\alpha = 0.8$. However, in this case also, our proposed methodology has been able to reduce this enhanced number of false positives quite effectively.

Finally, we have explored the idea of improving the number of TPs by incorporating little prior biological knowledge into the proposed methodology. The number of FPs remains the same as in the

case of individual datasets with $\alpha = 0.8$. But, we can infer a higher number of TPs, thus improving the overall quality measures like *specificity* and *accuracy* further. Thus, it can be concluded that the present approach can achieve its primary objective of reduction of FPs, while, with the help of some special endeavours we can improve the number of inferred TPs also, thus improving the overall quality of the reverse engineering endeavour.

Last but not the least, we would like to share our observations regarding the dataset ensemble approach, and its capability of FP reduction in comparison to our proposed methodology of model/technique combination. We did not find the dataset ensemble approach to be superior to our proposed methodology of model/technique aggregation. The number of FPs did diminish on combining multiple datasets for any particular model/technique. However, the number of TPs also took a severe hit.

The plausible reason behind this may be the fact that different datasets may have contained different amounts of environmental/experimental noise under different experimental setups. Thus, any swarm intelligence technique based model may not give consistent results across all the datasets. It is obvious that if it performs poorly even for a single dataset, the accuracy of the predicted ensemble network deteriorates. On the contrary, our proposed methodology of model ensemble requires only a single dataset. Thus, the two approaches cannot be directly compared. Nevertheless, we can observe that the results from the dataset ensemble approach do not compare favourably (in most of the cases) to our proposed methodology of technique amalgamation (for any particular dataset).

In the future, for large-scale GRN construction, the proposed methodology can be integrated into other improved methods (Marbach et al., 2012), to further improve/enhance the results. This will be able to achieve significant reduction in false positives, and thus, increase the overall quality of the inferred large-scale networks.

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