Gene Regulatory Networks Modelling using a Dynamic Evolutionary Hybrid

Ioannis A Maraziotis, Andrei Dragomir and Dimitris Thanos

Supplementary Material

In this paper we proposed a method for GRN reconstruction, based on a hybrid neural network structure named ENFRN. The inferred interactions originate from ENFRN structures. After those structures are trained on a specific dataset on a certain microarray experiment they can be tested against any other dataset (containing of course the same sets of genes) hence allowing to check for consistencies or inconsistencies among different biological experiments.

In this Supplementary Material we include several tables and figures concerning the parameters of the method, the inferred interactions, comparison with other methods in terms of GRN reconstruction and corresponding computational times. Given the stochastic nature of PSO, in all of the conducted experiments the simplification and training stages have been repeated for 5 times and the mean of the results are reported.

Tables (3,5,7,9,11) provide information regarding the extracted interactions. Those tables present the regulator and target genes, the composite score of the network on the test set used and the kind of biological knowledge (genetic, physical, intermediate, or none) that backs up the interaction. Tables (2,4,6,8,10) present the composite score levels at the 3 phases of learning and training, as well as the number of rules and output nodes in the initial and simplified structures. Figures (2,3,5) present the reconstructed networks when subset \textit{cdc28} was used for testing in the three different data groups (8 histones, 19 genes group and Chen’s – 41 genes, respectively).

As it can be noticed (see section \textit{Determining Potential Regulators} section in the main manuscript), the composite score is an integrative measure indicating on the one hand the ability of the input variable(s) to predict the output signal and on the other the coherency concerning the expressional status alterations of output in comparison to the input (see \textit{From ENFRN structure to Regulation Type} subsection in the main manuscript). The composite score of an interaction is the criterion based on which we decide whether or not we consider an interaction as valid. The lower the score of a certain interaction is, the more certain we can be of its validity.

In section ‘Methods’ of the main manuscript we describe the ENFRN training process composed of three learning phases. Those phases are initial structure creation, simplification phase and finally fine-tuning of the ENFRN weights and parameters. A general point of caution in every Neural Network based approach is the one concerning over-training of the network that can lead to over-fitting and thus to networks with poor generalization properties. Therefore, we have allowed a larger value of composite score during training, and thus ENFRN models manage to better fit the unseen data. Indeed as
we can depict in Fig. (4) in the majority of the cases the score of the extracted interaction is smaller in the testing set (mean composite score equal to 0.32) than the one of the training set (mean composite score equal to 0.30).

In Figure 6, we show the composite score distributions for the smallest (8 genes) and largest (41 genes) of the networks we reconstructed. As we can deduce from the figure the majority of the composite scores in the first case is between 0.5 and 0.6, while in the latter all the composite scores have values smaller than 0.5. However, as it can be noticed from the tables presenting the respective interactions, in both cases the vast majority of the inferred relations among genes correspond to biologically validated interactions. This indicates the flexibility of the proposed method over the input dataset. Indeed, it is shown that the method will adequately manage to determine the best interactions following the peculiarities of the input data, while the composite scores will allow the user to evaluate the significance of the inferred interactions and select the ones with the lower values.

A highly important aspect for every method applied to the problem at hand is the one concerning the time needed for reconstructing a certain network. We have mentioned that an advantage of the proposed methodology in terms of computational efficiency, concerns the first 2 stages of the general reconstructing framework described in section ‘Determining Potential Regulators’ and Figure 7 of the main manuscript. We have tested experimentally the computational efficiency of this part by randomly selecting sets of genes (from the same dataset we have used thought out this paper) whose number of members was ranging from 5 to 150 genes. We recorded the time it took the method to conclude the first 2 stages of the proposed reconstruction framework. Although, as we can deduce from Figure 7, the processing time follows an exponential increase with the size of genes sets, still the processing time is very low (it took less than 2.5 minutes to reconstruct the initial structure of 150 genes). These two stages of the reconstruction framework use the first phase of ENFRN training. Given that an ENFRN structure initially created by the first phase of the training process will be later pruned by the Structure Optimization phase we do not need to pay special attention in the parameters regarding the centers, widths and overlapping degrees of the fuzzy sets for the input and output variables. Hence we can set these parameters to low values (Table 1) to ensure an especially detailed initial structure (large number of rules and output nodes) that will be pruned later. The low values of these parameters will allow a coarse but accurate first estimate concerning the candidate regulators for every gene, which will be later refined.

Following we will discuss the total time the method needs to fully complete its operation and output the final reconstructed GRN, by commenting on the results presented in Table 12. Two especially important parameters of the proposed methodology are the number of BPSO and PSO particles used for simplification and fine-tuning. The larger the number of those particles the more time the algorithm will need to output the reconstructed network. In Table 12 we present results regarding the accuracy and computational processing time of the proposed methodology under different experimental setups regarding the two previously mentioned parameters, as well as comparisons to other methods. Prior continuing, we should note that timings are inevitably not only machine-dependent but also depended on various implementation and code optimizations techniques. Nevertheless, in Table 12 we present indicative of the relative timings, for the
algorithms we have used to compare our method with. All the methods (including ENFRN) have been implemented in Matlab© and run on a QUAD 2.6 GHz with 4 Gb RAM machine. As seen in Table 12, ENFRN based method had significantly better performance over the other algorithms in terms of both biological validity of the results and computational efficiency.

A first conclusion that can be drawn from Table 12 as well as Table 3 of the main manuscript, is that our method managed to significantly outperform all of the 3 methods we have used for comparison. Inspection of Table 12, proves that the proposed ENFRN-based approach is much more efficient than DN, DBN and RSONFIN in terms of computational time needed for the methods to fully reconstruct a certain GRN.

The results obtained when using 10 and 20 particles are similar both in outcome and time. This is mainly due to the number of iterations we allow PSO and BPSO to run without breaking their operation. By increasing this value and the number of particles we could end up with better values of training composite scores. A strategy such as this though would lead to overtraining of ENFRN and thus produce poor results when applied to unknown data.

The adequate results of the method, despite the small number of particles and training epochs for PSO (in comparison to other methods [4]) prove the efficiency of the algorithm responsible for creating the initial structure of ENFRN, as well as the proficient application of fuzzy logic and recurrent mechanism when applied to the intrinsic problem of GRN reconstruction.

As a final comment concerning the computational time needed for GRN reconstruction using the proposed approach, we should emphasize the fact that the method followed to infer the regulators of every gene present in a dataset can (in contrast to other methods like BNs and DBNs) be easily implemented using parallel techniques of processing. A framework such as this will allow the method to be feasibly applicable to much larger datasets.

| ENFRN Parameters                              | Values   |
|-----------------------------------------------|----------|
| Minimum Distance for Rule Node Creation ($F_{in}$) | 0.01     |
| Minimum Distance for Output Node Creation ($F_{out}$) | 0.01     |
| Overlapping degree of input and output clusters ($\delta$) | 0.05     |
| Number of particles for training in PSO       | 5        |
| Number of particles for simplification in BPSO | 5        |
| Allowed Iterations for PSO and BPSO           | 20       |
| Stop PSO and BPSO if no improvement after a number of iterations | 5        |

*Table 1*: Values for the parameters of ENFRN models used in this study.
1. 8 Histones Group

A. alpha

Figure 1: The number of rules and output nodes before and after the simplification process, based on the 16 ENFRN models describing the 16 interactions determined for the 8 histones, on alpha subset.

B. cdc28

| a/a | Regulator Target | Composite Error Values in ENFRN Structures | Number of Rules and Output Nodes in ENFRN Structures |
|-----|------------------|------------------------------------------|------------------------------------------------------|
|     |                  | Initial | Simplified | Trained | Rules | Output | Rules | Output |
| 1   | HTB1             | 0.899   | 0.935      | 0.533   | 12    | 9      | 12    | 9      |
| 2   | HHF1             | 1.127   | 1.127      | 0.712   | 10    | 9      | 10    | 9      |
| 3   | HTB1             | 0.842   | 0.815      | 0.536   | 12    | 8      | 10    | 8      |
| 4   | HHF2             | 1.127   | 1.127      | 0.712   | 10    | 9      | 10    | 9      |
| 5   | HHF2             | 0.657   | 0.669      | 0.543   | 14    | 10     | 12    | 10     |
| 6   | HHT1             | 0.898   | 0.916      | 0.664   | 12    | 9      | 10    | 9      |
| 7   | HTB2             | 0.877   | 0.877      | 0.743   | 11    | 10     | 10    | 10     |
| 8   | HHT2             | 1.127   | 1.127      | 0.712   | 10    | 9      | 10    | 9      |
| 9   | HTB2             | 0.981   | 0.981      | 0.673   | 11    | 9      | 10    | 9      |
| 10  | HHF2             | 0.890   | 0.881      | 0.589   | 14    | 10     | 13    | 10     |
| 11  | HHT2             | 0.962   | 0.975      | 0.749   | 14    | 10     | 10    | 9      |
### Table 2: Information on ENFRN models that extracted the interactions

| a/a  | Regulator | Target | Type | Composite Score | Genetic Interaction | Physical Interaction | Intermediate Connection |
|------|-----------|--------|------|-----------------|---------------------|----------------------|------------------------|
| 1.   | HTB1      | HTA1   | +    | 0.43403         | 1                   | 1                    | -                      |
| 2.   | HHF1      | HTA1   | -    | 0.56429         | 1                   | 1                    | -                      |
| 3.   | HTB1      | HHF1   | +    | 0.58183         | 1                   | 1                    | -                      |
| 4.   | HHF2      | HTA1   | -    | 0.49662         | 1                   | 1                    | -                      |
| 5.   | HHF2      | HTA2   | -    | 0.51812         | 0                   | 1                    | -                      |
| 6.   | HHT1      | HTA1   | +    | 0.56794         | 1                   | 1                    | -                      |
| 7.   | HTB2      | HHT1   | +    | 0.59228         | 0                   | 1                    | -                      |
| 8.   | HHT2      | HTA1   | -    | 0.50463         | 1                   | 1                    | -                      |
| 9.   | HTB2      | HHT2   | +    | 0.58642         | 0                   | 0                    | -                      |
| 10.  | HHF2      | HHT2   | +    | 0.40183         | 1                   | 1                    | -                      |
| 11.  | HHT2      | HHT1   | +    | 0.54196         | 1                   | 1                    | -                      |

#### Table 3: Interactions extracted

8 out of the 11 interactions have been identified as both genetic and physical interactions while 2 more as strictly physical, thus providing more than 90% of the interactions backed up by biological evidence.

![Extracted network for the 8 histones, based on cdc28 test data set.](image-url)

**Figure 2:** Extracted network for the 8 histones, based on cdc28 test data set.
## 2. 19 genes Group

### A. Alpha

| a/a | Regulator | Target | Composite Score Values in ENFRN Structures | Number of Rules and Output Nodes in ENFRN Structures |
|-----|-----------|--------|-------------------------------------------|------------------------------------------------------|
|     |           |        | Initial Simplified Trained                | Rules Output Rules Output |
| 1   | CLB6      | RAD53  | 1.015 1.015 0.428 | 2 2 2 2 |
| 2   | CLB6      | CLB5   | 1.33 1.33 0.491  | 3 2 3 2 |
| 3   | POL12     | MCD1   | 0.634 0.634 0.491 | 3 2 3 2 |
| 4   | POL30     | MSH2   | 0.799 0.769 0.741 | 11 6 7 6 |
| 5   | PRI1      | MSH2   | 0.518 0.393 0.819 | 19 13 15 10 |
| 6   | MSH6      | MSH2   | 0.729 0.447 0.587 | 18 12 15 11 |
| 7   | POL12     | CDC45  | 0.498 0.748 0.737 | 3 2 3 2 |
| 8   | CDC45     | CLB5   | 1.33 1.33 0.491  | 3 2 3 2 |
| 9   | RAD53     | PDS1   | 1.44 0.683 0.48  | 4 4 3 3 |
| 10  | PDS1      | CLB5   | 1.33 1.33 0.491  | 3 2 3 2 |
| 11  | MCD1      | PDS1   | 1.48 0.683 0.48  | 4 4 3 3 |
| 12  | ASF1      | MSH2   | 0.808 0.541 0.771 | 18 12 11 8 |
| 13  | ASF1      | CDC45  | 0.908 0.887 0.735 | 18 3 15 3 |
| 14  | POL30     | POL2   | 0.446 0.344 0.648 | 18 14 14 11 |
| 15  | MSH6      | POL2   | 0.446 0.344 0.648 | 18 14 14 11 |
| 16  | PMS1      | POL2   | 0.434 0.432 0.76  | 21 16 13 9 |
| 17  | POL30     | HPR5   | 1.18 1.03 0.82  | 11 4 6 4 |
| 18  | PRI1      | HPR5   | 0.79 0.995 0.782 | 15 5 11 4 |
| 19  | RFA3      | HPR5   | 0.56 0.75 0.65  | 16 8 14 8 |
| 20  | PMS1      | HPR5   | 0.599 0.582 0.65 | 15 7 12 7 |
| 21  | PRI2      | POL12  | 0.4923 0.4923 0.7185 | 13 7 13 7 |

*Table 4: Information on ENFRN models that extracted the interactions*
| a/a | Regulator | Target | Type | Test Composite Score | Genetic Interaction | Physical Interaction | Intermediate Connection |
|-----|-----------|--------|------|----------------------|---------------------|----------------------|------------------------|
| 1   | CLB6      | RAD53  | +    | 0.36501              | 1                   | 0                    | -                      |
| 2   | CLB6      | CLB5   | +    | 0.26469              | 1                   | 0                    | -                      |
| 3   | POL12     | MCD1   | +    | 0.4641               | 0                   | 0                    | -                      |
| 4   | POL30     | MSH2   | -    | 0.61536              | 1                   | 1                    | -                      |
| 5   | PRI1      | MSH2   | -    | 0.525                | 1                   | 0                    | -                      |
| 6   | MSH6      | MSH2   | +    | 0.43607              | 1                   | 1                    | -                      |
| 7   | POL12     | CDC45  | +    | 0.56187              | 0                   | 0                    | -                      |
| 8   | CDC45     | CLB5   | +    | 0.28331              | 1                   | 0                    | -                      |
| 9   | RAD53     | PDS1   | +    | 0.35728              | 1                   | 0                    | -                      |
| 10  | PDS1      | CLB5   | +    | 0.36518              | 1                   | 1                    | -                      |
| 11  | MCD1      | PDS1   | +    | 0.37814              | 1                   | 0                    | -                      |
| 12  | ASF1      | MSH2   | -    | 0.47243              | 1                   | 0                    | -                      |
| 13  | ASF1      | CDC45  | -    | 0.65332              | 1                   | 0                    | -                      |
| 14  | POL30     | POL2   | +    | 0.55725              | 1                   | 0                    | -                      |
| 15  | MSH6      | POL2   | +    | 0.54639              | 1                   | 0                    | -                      |
| 16  | PMS1      | POL2   | +    | 0.59536              | 1                   | 0                    | -                      |
| 17  | POL30     | HPR5   | +    | 0.60493              | 1                   | 1                    | -                      |
| 18  | PRI1      | HPR5   | +    | 0.64222              | 1                   | 0                    | -                      |
| 19  | RFA3      | HPR5   | +    | 0.53237              | 0                   | 0                    | -                      |
| 20  | PMS1      | HPR5   | +    | 0.61444              | 0                   | 0                    | -                      |
| 21  | PRI2      | POL12  | +    | 0.59808              | 0                   | 1                    | -                      |

**Table 5**: Interactions extracted

**B. cdc28**

| a/a | Regulator | Target | Composite Score Values in ENFRN Structures | Number of Rules and Output Nodes in ENFRN Structures |
|-----|-----------|--------|--------------------------------------------|--------------------------------------------------|
|     |           |        | Initial | Simplified | Trained | Rules | Output | Rules | Output | Simplified | Output |
| 1   | POL12     | PRI2   | 0.952   | 0.952      | 0.710   | 3     | 2      | 3     | 2      |            |
| 2   | CLB6      | CLB5   | 1.330   | 1.330      | 0.491   | 3     | 2      | 3     | 2      |            |
| 3   | POL12     | MCD1   | 0.634   | 0.634      | 0.491   | 3     | 2      | 3     | 2      |            |
| 4   | POL30     | MSH2   | 0.799   | 0.769      | 0.741   | 11    | 6      | 7     | 6      |            |
| 5   | PRI1      | MSH2   | 0.518   | 0.393      | 0.819   | 19    | 13     | 15    | 10     |            |
| 6   | CDC45     | CLB5   | 1.330   | 1.330      | 0.491   | 3     | 2      | 3     | 2      |            |
| 8   | PMS1      | MSH2   | 0.830   | 0.717      | 0.577   | 15    | 11     | 13    | 10     |            |
| 9   | RAD53     | PDS1   | 2.840   | 0.683      | 0.480   | 4     | 4      | 3     | 3      |            |
| 10  | PDS1      | CLB5   | 1.330   | 1.330      | 0.491   | 3     | 2      | 3     | 2      |            |
| 11  | MCD1      | PDS1   | 2.160   | 0.585      | 0.455   | 5     | 5      | 4     | 4      |            |
| 12  | ASF1      | MSH2   | 0.729   | 0.447      | 0.587   | 18    | 12     | 15    | 11     |            |
| 13  | PRI1      | RAD54  | 0.612   | 0.661      | 0.983   | 20    | 12     | 14    | 8      |            |
| 14  | CDC45     | RAD54  | 0.976   | 0.974      | 0.898   | 15    | 11     | 14    | 11     |            |
| 15  | ASF1      | RAD54  | 0.976   | 0.974      | 0.898   | 15    | 11     | 14    | 11     |            |
| 16  | POL30     | POL2   | 0.446   | 0.344      | 0.648   | 18    | 14     | 14    | 11     |            |
| 17  | MSH6      | POL2   | 0.446   | 0.344      | 0.648   | 18    | 14     | 14    | 11     |            |
| 18  | PMS1      | POL2   | 0.434   | 0.432      | 0.760   | 21    | 16     | 13    | 9      |            |
| 19  | RFA3      | HPR5   | 0.560   | 0.750      | 0.650   | 16    | 8      | 14    | 8      |            |
Table 6: Information on ENFRN models that extracted the interactions

| a/a | Regulator | Target | Type | Test Total Score | Genetic Interaction | Physical Interaction | Intermediate Connection |
|-----|-----------|--------|------|------------------|---------------------|----------------------|------------------------|
| 1.  | POL12     | PRI2   | +    | 0.43466          | 0                   | 1                    | -                      |
| 2.  | CLB6      | CLB5   | +    | 0.41068          | 1                   | 0                    | -                      |
| 3.  | POL12     | MCD1   | +    | 0.39557          | 0                   | 0                    | -                      |
| 4.  | POL30     | MSH2   | -    | 0.65296          | 1                   | 1                    | -                      |
| 5.  | PRI1      | MSH2   | -    | 0.64373          | 1                   | 0                    | -                      |
| 6.  | MSH6      | MSH2   | +    | 0.54989          | 1                   | 1                    | -                      |
| 7.  | CDC45     | CLB5   | +    | 0.46271          | 1                   | 0                    | -                      |
| 8.  | PMS1      | MSH2   | +    | 0.65298          | 1                   | 1                    | -                      |
| 9.  | RAD53     | PDS1   | +    | 0.59583          | 1                   | 0                    | -                      |
| 10. | PDS1      | CLB5   | +    | 0.55971          | 1                   | 1                    | -                      |
| 11. | MCD1      | PDS1   | +    | 0.49503          | 1                   | 0                    | -                      |
| 12. | ASF1      | MSH2   | +    | 0.64932          | 1                   | 0                    | -                      |
| 13. | PRI1      | RAD54  | -    | 0.58412          | 1                   | 0                    | -                      |
| 14. | CDC45     | RAD54  | +    | 0.56406          | 1                   | 0                    | -                      |
| 15. | ASF1      | RAD54  | +    | 0.56405          | 1                   | 0                    | -                      |
| 16. | POL30     | POL2   | +    | 0.54795          | 1                   | 0                    | -                      |
| 17. | MSH6      | POL2   | +    | 0.61023          | 1                   | 0                    | -                      |
| 18. | PMS1      | POL2   | +    | 0.53604          | 1                   | 0                    | -                      |
| 19. | RFA3      | HPR5   | +    | 0.56684          | 0                   | 0                    | 2                      |

Table 7: Interactions extracted

16 out of the 19 interactions have been identified as genetic interactions while 1 more as strictly physical, thus providing more than 90% of the interactions backed up by biological evidence.

Figure 3: Extracted network for the 19 histones, based on cdc28 test data set.
### 3. Chen’s Data Set

#### A. Alpha

| a/a | Regulator | Target | Composite Score Values in ENFRN Structures | Number of Rules and Output Nodes in ENFRN Structures |
|-----|-----------|--------|--------------------------------------------|-----------------------------------------------------|
|     |           |        | Initial | Simplified | Trained | Initial | Simplified |
| 1   | SWI5      | FKH1   | 0.351   | 0.383      | 0.306   | 20      | 13        | 15        | 10        |
| 2   | SWI5      | PCL2   | 0.277   | 0.283      | 0.283   | 14      | 13        | 6         | 6         |
| 3   | STE12     | ASH1   | 0.324   | 0.324      | 0.311   | 10      | 8         | 10        | 8         |
| 4   | SPO12     | DBF2   | 0.246   | 0.301      | 0.3     | 11      | 7         | 6         | 5         |
| 5   | POG1      | CLN1   | 0.384   | 0.346      | 0.342   | 19      | 13        | 11        | 9         |
| 6   | HTB1      | REM1   | 0.245   | 0.245      | 0.218   | 6       | 5         | 6         | 5         |
| 7   | SWI4      | CLN1   | 0.33    | 0.348      | 0.289   | 23      | 16        | 16        | 12        |
| 8   | SWI4      | SPO12  | 0.344   | 0.344      | 0.532   | 13      | 6         | 13        | 6         |
| 9   | HHT1      | HTA1   | 0.295   | 0.295      | 0.281   | 13      | 10        | 13        | 10        |
| 10  | FKH1      | HHT1   | 0.266   | 0.266      | 0.263   | 16      | 12        | 16        | 12        |
| 11  | MOB1      | CLB6   | 0.324   | 0.324      | 0.319   | 14      | 9         | 14        | 9         |
| 12  | POG1      | CLB2   | 0.327   | 0.337      | 0.337   | 10      | 8         | 8         | 7         |
| 13  | CLN2      | CLN3   | 0.323   | 0.373      | 0.37    | 10      | 9         | 9         | 8         |
| 14  | CLN2      | CLN1   | 0.33    | 0.348      | 0.289   | 23      | 16        | 16        | 12        |
| 15  | MCM1      | CLB6   | 0.32    | 0.32       | 0.365   | 14      | 10        | 14        | 10        |
| 16  | SWI4      | HTA1   | 0.238   | 0.284      | 0.284   | 13      | 9         | 10        | 8         |
| 17  | MBP1      | SKN7   | 0.283   | 0.283      | 0.317   | 12      | 7         | 12        | 7         |
| 18  | NDD1      | YHP1   | 0.277   | 0.277      | 0.341   | 15      | 8         | 15        | 8         |
| 19  | OPY2      | CDC20  | 0.334   | 0.334      | 0.406   | 14      | 9         | 14        | 9         |
| 20  | MBP1      | SWI4   | 0.313   | 0.313      | 0.339   | 12      | 9         | 12        | 9         |
| 21  | FKH1      | HTA1   | 0.262   | 0.262      | 0.279   | 16      | 11        | 16        | 11        |
| 22  | CLN3      | YHP1   | 0.284   | 0.284      | 0.309   | 14      | 8         | 14        | 8         |
| 23  | CLN1      | SIC1   | 0.304   | 0.273      | 0.303   | 21      | 12        | 16        | 12        |
| 24  | PCL9      | SKN7   | 0.253   | 0.233      | 0.232   | 14      | 8         | 9         | 7         |
| 25  | MCM1      | YOX1   | 0.363   | 0.377      | 0.372   | 14      | 10        | 11        | 8         |
| 26  | POG1      | CLN2   | 0.214   | 0.214      | 0.268   | 19      | 9         | 19        | 9         |
| 27  | POG1      | ASH1   | 0.253   | 0.253      | 0.237   | 19      | 10        | 19        | 10        |
| 28  | HCM1      | MCM1   | 0.283   | 0.283      | 0.54    | 17      | 8         | 17        | 8         |
| 29  | SWI5      | CLB2   | 0.454   | 0.454      | 0.161   | 2       | 2         | 2         | 2         |
| 30  | FKH2      | CDC20  | 0.395   | 0.395      | 0.337   | 14      | 10        | 14        | 10        |
| 31  | PCL7      | CLB2   | 0.385   | 0.327      | 0.327   | 13      | 10        | 4         | 4         |
| 32  | YHP1      | SWI1   | 0.262   | 0.262      | 0.304   | 13      | 10        | 13        | 10        |
| 33  | SWI1      | MFA2   | 0.283   | 0.359      | 0.359   | 8       | 8         | 7         | 7         |
| 34  | CLB2      | FKH1   | 0.351   | 0.383      | 0.306   | 20      | 13        | 15        | 10        |
| 35  | MCM1      | YHP1   | 0.437   | 0.362      | 0.362   | 7       | 6         | 6         | 5         |
| 36  | SWI4      | SWI5   | 0.311   | 0.311      | 0.308   | 13      | 11        | 13        | 11        |
| 37  | FAR1      | CLB1   | 0.398   | 0.398      | 0.442   | 14      | 12        | 14        | 12        |
| 38  | SIC1      | SVS1   | 0.247   | 0.247      | 0.331   | 13      | 10        | 13        | 10        |
|   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|
| 39 | PCL2 | SWI5 | 0.325 | 0.351 | 0.351 | 13 | 11 |
| 40 | CLN2 | SWI4 | 0.27 | 0.266 | 0.29 | 22 | 14 |
| 41 | DBF2 | SWI5 | 0.282 | 0.276 | 0.322 | 23 | 17 |
| 42 | CLB2 | SWE1 | 0.387 | 0.449 | 0.449 | 10 | 6 |
| 43 | CLB2 | NDD1 | 0.321 | 0.284 | 0.284 | 16 | 10 |
| 44 | ASH1 | HCMI | 0.288 | 0.288 | 0.4 | 11 | 10 |
| 45 | CLB1 | CLN2 | 0.012 | 0.012 | 0.01 | 2 | 2 |
| 46 | PCL9 | HCMI | 0.308 | 0.308 | 0.414 | 14 | 9 |
| 47 | SWI4 | PCL7 | 0.283 | 0.299 | 0.299 | 14 | 12 |
| 48 | CLB1 | ASH1 | 0.097 | 0.097 | 0.086 | 2 | 2 |
| 49 | FAK1 | CLB2 | 0.476 | 0.539 | 0.539 | 5 | 5 |
| 50 | NDD1 | FKH2 | 0.431 | 0.431 | 0.329 | 15 | 9 |
| 51 | SIM1 | HHT1 | 0.253 | 0.253 | 0.285 | 17 | 11 |
| 52 | HTA1 | SKN7 | 0.252 | 0.252 | 0.275 | 12 | 9 |
| 53 | SIC1 | CLN3 | 0.265 | 0.278 | 0.293 | 22 | 14 |
| 54 | CDC20 | CLB2 | 0.345 | 0.301 | 0.301 | 12 | 10 |
| 55 | CLN1 | SWE1 | 0.322 | 0.322 | 0.247 | 16 | 11 |
| 56 | FKH1 | FKH2 | 0.366 | 0.395 | 0.39 | 16 | 10 |
| 57 | SVS1 | SKN7 | 0.245 | 0.245 | 0.295 | 15 | 10 |
| 58 | CLB2 | HCM1 | 0.338 | 0.373 | 0.373 | 10 | 7 |
| 59 | CLN3 | CLN1 | 0.33 | 0.348 | 0.289 | 23 | 16 |
| 60 | PCL2 | CLB4 | 0.277 | 0.364 | 0.364 | 12 | 8 |
| 61 | FKH1 | SWE1 | 0.263 | 0.263 | 0.303 | 16 | 13 |
| 62 | CLB1 | HCM1 | 0.106 | 0.106 | 0.091 | 2 | 2 |
| 63 | SPO12 | CLN2 | 0.211 | 0.211 | 0.313 | 11 | 8 |
| 64 | FKH2 | SPO12 | 0.335 | 0.335 | 0.407 | 14 | 7 |
| 65 | SWI5 | SIC1 | 0.314 | 0.332 | 0.401 | 22 | 12 |
| 66 | CLB2 | FKH2 | 0.3 | 0.31 | 0.352 | 21 | 12 |
| 67 | FKH2 | SWI5 | 0.282 | 0.276 | 0.322 | 23 | 17 |
| 68 | CLB1 | CLB2 | 0.437 | 0.437 | 0.137 | 2 | 2 |
| 69 | HHT1 | SWE1 | 0.248 | 0.248 | 0.274 | 13 | 9 |
| 70 | CLB2 | POG1 | 0.320 | 0.323 | 0.323 | 19 | 13 |
| 71 | DBF2 | CDC20 | 0.419 | 0.586 | 0.586 | 9 | 5 |
| 72 | MFA1 | CLB4 | 0.273 | 0.273 | 0.542 | 8 | 6 |
| 73 | HHT1 | MCM1 | 0.25 | 0.25 | 0.293 | 13 | 7 |
| 74 | HCMI | PCL2 | 0.345 | 0.345 | 0.38 | 17 | 9 |
| 75 | ASH1 | CLB2 | 0.335 | 0.368 | 0.368 | 12 | 9 |
| 76 | REM1 | NDD1 | 0.245 | 0.327 | 11 | 9 |
| 77 | CDC20 | SIC1 | 0.304 | 0.273 | 0.303 | 21 | 12 |
| 78 | DBF2 | MOB1 | 0.293 | 0.403 | 0.402 | 10 | 8 |
| 79 | CLB2 | REM1 | 0.276 | 0.322 | 12 | 8 |
| 80 | FKH2 | ASH1 | 0.271 | 0.271 | 0.314 | 14 | 11 |
| 81 | CLB1 | SVS1 | 0.069 | 0.069 | 0.069 | 2 | 2 |
| 82 | SWE1 | SIC1 | 0.38 | 0.441 | 0.439 | 15 | 11 |
| 83 | CLB6 | CLN3 | 0.301 | 0.301 | 0.303 | 16 | 10 |

Table 8: Information on ENFRN models that extracted the interactions
| a/a | Regulator | Target | Type | Test Composite Score | Genetic Interaction | Physical Interaction | Intermediate Connection |
|-----|-----------|--------|------|----------------------|---------------------|----------------------|------------------------|
| 1   | SWI5      | FKH1   | +    | 0.28839              | 1                   | 0                    | -                      |
| 2   | SWI5      | PCL2   | +    | 0.37271              | 0                   | 1                    | -                      |
| 3   | STE12     | ASH1   | +    | 0.27529              | 1                   | 0                    | -                      |
| 4   | SPO12     | DBF2   | +    | 0.31364              | 1                   | 0                    | -                      |
| 5   | POG1      | CLN1   | -    | 0.37537              | 1                   | 0                    | -                      |
| 6   | HTB1      | REM1   | +    | 0.23275              | 0                   | 0                    | -                      |
| 7   | SWI4      | CLN1   | +    | 0.26917              | 1                   | 0                    | -                      |
| 8   | SWI4      | SPO12  | -    | 0.35007              | 0                   | 0                    | 1                      |
| 9   | HHT1      | HTA1   | +    | 0.28732              | 1                   | 1                    | -                      |
| 10  | FKH1      | HHT1   | +    | 0.27241              | 1                   | 0                    | -                      |
| 11  | MOB1      | CLB6   | +    | 0.27041              | 1                   | 0                    | -                      |
| 12  | POG1      | CLB2   | +    | 0.32732              | 0                   | 1                    | -                      |
| 13  | CLN2      | CLN3   | -    | 0.37156              | 1                   | 0                    | -                      |
| 14  | CLN2      | CLN1   | +    | 0.26476              | 1                   | 0                    | -                      |
| 15  | MCM1      | CLB6   | +    | 0.26709              | 0                   | 0                    | -                      |
| 16  | SWI4      | HTA1   | +    | 0.25682              | 1                   | 0                    | -                      |
| 17  | MBP1      | SKN7   | +    | 0.29724              | 1                   | 1                    | -                      |
| 18  | NDD1      | YHP1   | +    | 0.28438              | 0                   | 0                    | -                      |
| 19  | OPY2      | CDC20  | +    | 0.28929              | 0                   | 0                    | -                      |
| 20  | MBP1      | SWI4   | -    | 0.32066              | 1                   | 0                    | -                      |
| 21  | FKH1      | HTA1   | +    | 0.24046              | 0                   | 0                    | -                      |
| 22  | CLN3      | YHP1   | +    | 0.28753              | 0                   | 0                    | -                      |
| 23  | CLN1      | SIC1   | +    | 0.30543              | 1                   | 1                    | -                      |
| 24  | PCL9      | SKN7   | +    | 0.25134              | 0                   | 0                    | -                      |
| 25  | MCM1      | YOX1   | -    | 0.34596              | 0                   | 1                    | -                      |
| 26  | POG1      | CLN2   | +    | 0.23723              | 0                   | 0                    | -                      |
| 27  | POG1      | ASH1   | +    | 0.25454              | 0                   | 0                    | -                      |
| 28  | HCM1      | MCM1   | +    | 0.25217              | 0                   | 0                    | -                      |
| 29  | SWI5      | CLB2   | +    | 0.17348              | 1                   | 1                    | -                      |
| 30  | FKH2      | CDC20  | -    | 0.38557              | 1                   | 0                    | -                      |
| 31  | PCL7      | CLB2   | +    | 0.38506              | 0                   | 1                    | -                      |
| 32  | YHP1      | SWE1   | +    | 0.25162              | 0                   | 0                    | -                      |
| 33  | SWE1      | MFA2   | +    | 0.28116              | 0                   | 1                    | -                      |
| 34  | CLB2      | FKH1   | +    | 0.27734              | 1                   | 0                    | -                      |
| 35  | MCM1      | YHP1   | +    | 0.43679              | 0                   | 1                    | -                      |
| 36  | SWI4      | SWI5   | -    | 0.32049              | 1                   | 0                    | -                      |
| 37  | FAR1      | CLB1   | +    | 0.44146              | 0                   | 0                    | 2                      |
| 38  | SIC1      | SVS1   | +    | 0.2578               | 0                   | 0                    | -                      |
| 39  | PCL2      | SWI5   | +    | 0.32467              | 0                   | 1                    | -                      |
| 40  | CLN2      | SWI4   | +    | 0.26381              | 1                   | 0                    | -                      |
| 41  | DBF2      | SWI5   | -    | 0.30345              | 1                   | 0                    | -                      |
| 42  | CLB2      | SWI1   | +    | 0.38686              | 0                   | 1                    | -                      |
| 43  | CLB2      | NDD1   | +    | 0.43184              | 0                   | 1                    | -                      |
| 44  | ASH1      | HCM1   | +    | 0.27064              | 0                   | 0                    | -                      |
| 45  | CLB1      | CLN2   | +    | 0.02778              | 0                   | 0                    | -                      |
| 46  | PCL9      | HCM1   | +    | 0.31231              | 0                   | 0                    | 2                      |
| 47  | SWI4      | PCL7   | +    | 0.27128              | 0                   | 1                    | -                      |
| 48  | CLB1      | ASH1   | +    | 0.02783              | 0                   | 0                    | -                      |
|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 49 | FAR1 | CLB2 | + | 0.47576 | 0 | 1 | - |
| 50 | NDD1 | FKH2 | - | 0.39547 | 1 | 1 | - |
| 51 | SIM1 | HHT1 | + | 0.26507 | 0 | 0 | - |
| 52 | HTA1 | SKN7 | + | 0.28093 | 0 | 0 | - |
| 53 | SRC1 | CLN3 | - | 0.29585 | 1 | 1 | - |
| 54 | CDC20 | CLB2 | + | 0.34488 | 0 | 1 | - |
| 55 | CLN1 | SWE1 | + | 0.29513 | 1 | 0 | - |
| 56 | FKH1 | FKH2 | - | 0.38863 | 1 | 0 | - |
| 57 | SVS1 | SKN7 | + | 0.26282 | 0 | 0 | - |
| 58 | CLB2 | HCM1 | + | 0.33834 | 0 | 1 | - |
| 59 | CLN3 | CLN1 | + | 0.27146 | 1 | 0 | - |
| 60 | PCL2 | CLB4 | + | 0.35189 | 0 | 0 | 2 |
| 61 | FKH1 | SWE1 | + | 0.25435 | 0 | 0 | - |
| 62 | CLB1 | HCM1 | + | 0.02046 | 0 | 0 | 2 |
| 63 | SPO12 | CLN2 | + | 0.23563 | 0 | 0 | 1 |
| 64 | FKH2 | SPO12 | + | 0.34023 | 0 | 0 | 1 |
| 65 | SW15 | SIC1 | + | 0.35223 | 1 | 0 | - |
| 66 | CLB2 | FKH2 | + | 0.30509 | 1 | 1 | - |
| 67 | FKH2 | SW15 | - | 0.30795 | 1 | 0 | - |
| 68 | CLB1 | CLB2 | + | 0.07883 | 1 | 1 | - |
| 69 | HHT1 | SWE1 | + | 0.22974 | 0 | 0 | - |
| 70 | CLB2 | POG1 | + | 0.37187 | 0 | 1 | - |
| 71 | DBF2 | CDC20 | + | 0.41944 | 0 | 1 | - |
| 72 | MFA1 | CLB4 | + | 0.28162 | 0 | 0 | - |
| 73 | HHT1 | MCM1 | + | 0.2581 | 0 | 0 | - |
| 74 | HCM1 | PCL2 | + | 0.37284 | 0 | 0 | 2 |
| 75 | ASH1 | CLB2 | + | 0.33469 | 0 | 1 | - |
| 76 | REM1 | NDD1 | + | 0.255 | 0 | 0 | - |
| 77 | CDC20 | SIC1 | + | 0.30354 | 1 | 0 | - |
| 78 | DBF2 | MOB1 | - | 0.42495 | 1 | 1 | - |
| 79 | CLB2 | REM1 | - | 0.34541 | 1 | 0 | - |
| 80 | FKH2 | ASH1 | + | 0.28332 | 0 | 0 | - |
| 81 | CLB1 | SVS1 | + | 0.03096 | 0 | 0 | - |
| 82 | SWE1 | SIC1 | - | 0.38071 | 1 | 0 | - |
| 83 | CLB6 | CLN3 | - | 0.30596 | 1 | 0 | - |

Table 9: Interactions extracted
**Figure 4**: Test Vs Training composite scores for Chen’s Data set – testing in *alpha* data set.

**B. cdc28**

| a/a | Reg  | Targ  | Composite Score Values in ENFRN Structures | Number of Rules and Output Nodes in ENFRN Structures |
|-----|------|-------|---------------------------------------------|-----------------------------------------------------|
|     |      |       | Initial | Simplified | Trained | Rules | Output Rules | Output |
| 1   | DBF2 | CDC20 | 0.419   | 0.586     | 0.586   | 9     | 5             | 4      | 3     |
| 2   | PCL2 | SWI5  | 0.325   | 0.351     | 0.351   | 13    | 11            | 10     | 9     |
| 3   | SW14 | CLN1  | 0.33    | 0.348     | 0.289   | 23    | 16            | 16     | 12    |
| 4   | HTT1 | HTA1  | 0.295   | 0.295     | 0.281   | 13    | 10            | 13     | 10    |
| 5   | FKH2 | CDC20 | 0.395   | 0.395     | 0.337   | 14    | 10            | 14     | 10    |
| 6   | MBP1 | SWI4  | 0.313   | 0.313     | 0.339   | 12    | 9             | 12     | 9     |
| 7   | CDC20| CLB2  | 0.345   | 0.301     | 0.301   | 12    | 10            | 9      | 7     |
| 8   | CLN2 | SWI4  | 0.27    | 0.266     | 0.29    | 22    | 14            | 17     | 14    |
| 9   | SW14 | HTA1  | 0.238   | 0.284     | 0.284   | 13    | 9             | 10     | 8     |
| 10  | ASH1 | HCM1  | 0.288   | 0.288     | 0.4     | 11    | 10            | 11     | 10    |
| 11  | POG1 | CLN1  | 0.384   | 0.346     | 0.342   | 19    | 13            | 11     | 9     |
| 12  | SIM1 | MOB1  | 0.278   | 0.278     | 0.273   | 17    | 11            | 17     | 11    |
| 13  | POG1 | ASH1  | 0.253   | 0.253     | 0.237   | 19    | 10            | 19     | 10    |
| 14  | CLB1 | CLB2  | 0.437   | 0.437     | 0.137   | 2     | 2             | 2      | 2     |
| 15  | SW15 | FKH1  | 0.318   | 0.318     | 0.32    | 17    | 12            | 17     | 12    |
| 16  | PCL9 | HCM1  | 0.308   | 0.308     | 0.414   | 14    | 9             | 14     | 9     |
| 17  | DBF2 | MOB1  | 0.293   | 0.403     | 0.402   | 10    | 8             | 5      | 4     |
|   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|
| 18 | SWI5 | SIC1 | 0.314 | 0.332 | 0.401 | 22 | 12 |
| 19 | SPO12 | DBF2 | 0.246 | 0.301 | 0.3 | 11 | 7 |
| 20 | SIC1 | SVS1 | 0.247 | 0.247 | 0.331 | 13 | 10 |
| 21 | MBP1 | SKN7 | 0.283 | 0.283 | 0.317 | 12 | 7 |
| 22 | MCM1 | YOX1 | 0.363 | 0.377 | 0.372 | 14 | 10 |
| 23 | CLB2 | SWE1 | 0.387 | 0.449 | 0.449 | 10 | 6 |
| 24 | SPO12 | CLN2 | 0.211 | 0.211 | 0.313 | 11 | 8 |
| 25 | SWI5 | PCL2 | 0.277 | 0.283 | 0.283 | 14 | 13 |
| 26 | SWI4 | PCL7 | 0.283 | 0.299 | 0.299 | 14 | 12 |
| 27 | MFA1 | MBP1 | 0.318 | 0.318 | 0.548 | 8 | 5 |
| 28 | CLB1 | CLN2 | 0.012 | 0.012 | 0.01 | 2 | 2 |
| 29 | CLB1 | SVS1 | 0.069 | 0.069 | 0.069 | 2 | 2 |
| 30 | SWI4 | FAR1 | 0.309 | 0.309 | 0.355 | 13 | 11 |
| 31 | FKH1 | HTA1 | 0.262 | 0.262 | 0.279 | 16 | 11 |
| 32 | FKH1 | HHT1 | 0.266 | 0.266 | 0.263 | 16 | 12 |
| 33 | CLB2 | NDD1 | 0.321 | 0.284 | 0.284 | 16 | 10 |
| 34 | SWI4 | MFA2 | 0.283 | 0.359 | 0.359 | 8 | 8 |
| 35 | POG1 | MN1 | 0.258 | 0.258 | 0.29 | 19 | 14 |
| 36 | HCM1 | PCL2 | 0.345 | 0.345 | 0.38 | 17 | 9 |
| 37 | CLB2 | HCM1 | 0.338 | 0.373 | 0.373 | 10 | 7 |
| 38 | CLB2 | FKH1 | 0.351 | 0.383 | 0.306 | 20 | 13 |
| 39 | STE12 | ASH1 | 0.324 | 0.324 | 0.311 | 10 | 8 |
| 40 | POG1 | CLB2 | 0.327 | 0.337 | 0.337 | 10 | 8 |
| 41 | CLB2 | POG1 | 0.302 | 0.323 | 0.323 | 19 | 13 |
| 42 | FKH1 | FKH2 | 0.366 | 0.395 | 0.39 | 16 | 10 |
| 43 | CLN3 | CLN1 | 0.33 | 0.34 | 0.289 | 10 | 9 |
| 44 | CLN2 | CLN1 | 0.33 | 0.34 | 0.289 | 10 | 9 |
| 45 | CLB6 | CLN3 | 0.301 | 0.301 | 0.303 | 10 | 16 |
| 46 | PCL9 | SKN7 | 0.253 | 0.233 | 0.232 | 14 | 8 |
| 47 | CLB1 | ASH1 | 0.097 | 0.097 | 0.086 | 2 | 2 |
| 48 | CLB2 | FKH2 | 0.3 | 0.31 | 0.352 | 21 | 12 |
| 49 | ASH1 | CLB2 | 0.335 | 0.368 | 0.368 | 12 | 9 |
| 50 | CLN2 | CLN3 | 0.323 | 0.373 | 0.37 | 10 | 9 |
| 51 | CLN3 | YHP1 | 0.284 | 0.284 | 0.309 | 14 | 8 |
| 52 | SWE1 | SIC1 | 0.38 | 0.441 | 0.439 | 15 | 11 |
| 53 | NDD1 | FKH2 | 0.431 | 0.431 | 0.329 | 15 | 9 |
| 54 | CLB2 | REM1 | 0.276 | 0.324 | 0.322 | 12 | 8 |
| 55 | CLN2 | FAR1 | 0.439 | 0.439 | 0.634 | 10 | 8 |
| 56 | PCL7 | CLB2 | 0.385 | 0.327 | 0.327 | 13 | 10 |
| 57 | HTB1 | REM1 | 0.245 | 0.245 | 0.218 | 6 | 5 |
| 58 | CDC20 | SIC1 | 0.304 | 0.273 | 0.303 | 21 | 12 |
| 59 | FAR1 | CLB2 | 0.476 | 0.539 | 0.539 | 5 | 5 |
| 60 | MCM1 | YHP1 | 0.437 | 0.362 | 0.362 | 7 | 6 |
| 61 | CLB1 | HCM1 | 0.106 | 0.106 | 0.091 | 2 | 2 |
| 62 | SWI4 | SWI5 | 0.311 | 0.311 | 0.308 | 13 | 11 |
| 63 | FKH2 | SWI5 | 0.282 | 0.276 | 0.322 | 23 | 17 |
| 64 | PCL2 | CLB4 | 0.277 | 0.364 | 0.364 | 12 | 8 |
| 65 | CLN1 | SWI5 | 0.322 | 0.322 | 0.247 | 16 | 11 |
| 66 | FKH2 | ASH1 | 0.271 | 0.271 | 0.314 | 14 | 11 |
| 67 | CLN1 | SIC1 | 0.304 | 0.273 | 0.303 | 21 | 12 |
| 68 | DBF2 | SWI5 | 0.282 | 0.276 | 0.322 | 23 | 17 |
| 69 | SIC1 | CLN3 | 0.265 | 0.278 | 0.293 | 22 | 14 |
| 70 | SWI5 | CLB2 | 0.454 | 0.454 | 0.161 | 2 | 2 |

Table 10: Information on ENFRN models that extracted the interactions
| a/a | Regulator | Target   | Type | Test Composite Score | Genetic Interaction | Physical Interaction | Intermediate Connection |
|-----|-----------|----------|------|----------------------|---------------------|----------------------|------------------------|
| 1   | DBF2      | CDC20    | +    | 0.41944              | 0                   | 1                    | -                      |
| 2   | PCL2      | SWI5     | +    | 0.32467              | 0                   | 1                    | -                      |
| 3   | SWI4      | CLN1     | +    | 0.27004              | 1                   | 0                    | -                      |
| 4   | HHT1      | HTA1     | +    | 0.35928              | 1                   | 1                    | -                      |
| 5   | FKH2      | CDC20    | -    | 0.49529              | 1                   | 0                    | -                      |
| 6   | MBP1      | SWI4     | -    | 0.32922              | 1                   | 0                    | -                      |
| 7   | CDC20     | CLB2     | +    | 0.34488              | 0                   | 1                    | -                      |
| 8   | CLN2      | SWI4     | +    | 0.28629              | 1                   | 0                    | -                      |
| 9   | SWI4      | HTA1     | +    | 0.32997              | 1                   | 0                    | -                      |
| 10  | ASH1      | HCM1     | +    | 0.27872              | 0                   | 0                    | -                      |
| 11  | POG1      | CLN1     | -    | 0.39697              | 1                   | 0                    | -                      |
| 12  | SIM1      | MOB1     | +    | 0.28704              | 0                   | 0                    | -                      |
| 13  | POG1      | ASH1     | +    | 0.2528               | 0                   | 0                    | -                      |
| 14  | CLB1      | CLB2     | +    | 0.14843              | 1                   | 1                    | -                      |
| 15  | SWI5      | FKH1     | -    | 0.4683               | 1                   | 0                    | -                      |
| 16  | PCL9      | HCM1     | +    | 0.35165              | 0                   | 0                    | 2                      |
| 17  | DBF2      | MOB1     | -    | 0.47922              | 1                   | 1                    | -                      |
| 18  | SWI5      | SIC1     | +    | 0.45409              | 1                   | 0                    | -                      |
| 19  | SPO12     | DBF2     | +    | 0.39346              | 1                   | 0                    | -                      |
| 20  | SIC1      | SVS1     | +    | 0.28185              | 0                   | 0                    | -                      |
| 21  | MBP1      | SKN7     | +    | 0.31302              | 1                   | 1                    | -                      |
| 22  | MCM1      | YOX1     | -    | 0.45419              | 0                   | 1                    | -                      |
| 23  | CLB2      | SWE1     | +    | 0.38686              | 0                   | 1                    | -                      |
| 24  | SPO12     | CLN2     | +    | 0.3465               | 0                   | 0                    | 1                      |
| 25  | SWI5      | PCL2     | +    | 0.37271              | 0                   | 1                    | -                      |
| 26  | SWI4      | PCL7     | +    | 0.27128              | 0                   | 1                    | -                      |
| 27  | MFA1      | MBP1     | +    | 0.2722               | 0                   | 0                    | -                      |
| 28  | CLB1      | CLN2     | +    | 0.14985              | 0                   | 0                    | -                      |
| 29  | CLB1      | SVS1     | +    | 0.07284              | 0                   | 0                    | -                      |
| 30  | SWI4      | FAR1     | +    | 0.30995              | 0                   | 0                    | 1                      |
| 31  | FKH1      | HTA1     | +    | 0.28757              | 0                   | 0                    | -                      |
| 32  | FKH1      | HHT1     | +    | 0.28763              | 0                   | 0                    | -                      |
| 33  | CLB2      | NDD1     | +    | 0.43184              | 0                   | 1                    | -                      |
| 34  | SWE1      | MFA2     | +    | 0.28116              | 0                   | 1                    | -                      |
| 35  | POG1      | MNN1     | +    | 0.25307              | 0                   | 0                    | -                      |
| 36  | HCM1      | PCL2     | +    | 0.41778              | 0                   | 0                    | 2                      |
| 37  | CLB2      | HCM1     | +    | 0.33834              | 0                   | 1                    | -                      |
| 38  | CLB2      | FKH1     | +    | 0.38064              | 1                   | 0                    | -                      |
| 39  | STE12     | ASH1     | +    | 0.28034              | 1                   | 0                    | -                      |
| 40  | POG1      | CLB2     | +    | 0.32732              | 0                   | 1                    | -                      |
| 41  | CLB2      | POG1     | +    | 0.37187              | 0                   | 1                    | -                      |
| 42  | FKH1      | FKH2     | -    | 0.4278               | 1                   | 0                    | -                      |
| 43  | CLN3      | CLN1     | +    | 0.27198              | 1                   | 0                    | -                      |
| 44  | CLN2      | CLN1     | +    | 0.27258              | 1                   | 0                    | -                      |
| 45  | CLB6      | CLN3     | -    | 0.3333               | 1                   | 0                    | -                      |
| 46  | PCL9      | SKN7     | +    | 0.26794              | 0                   | 0                    | -                      |
| 47  | CLB1      | ASH1     | +    | 0.02996              | 0                   | 0                    | -                      |
| 48  | CLB2      | FKH2     | +    | 0.36824              | 1                   | 1                    | -                      |
| 49  | ASH1      | CLB2     | +    | 0.33469              | 0                   | 1                    | -                      |
Table 11: Interactions extracted

We can deduce from Table 11 that the method has extracted 33 genetic interactions, and 16 solely physical interactions, 6 intermediate. So we have either 70% or 79% (with intermediate) from the interactions extracted to be in accordance with prior biological knowledge.
**Figure 5:** Extracted network for the Chen's data, based on cdc28 test data set.

**Figure 6:** Distribution of Composite Scores corresponding to the smallest (8 genes - left) and largest (41 genes - right) of all datasets we have used to reconstruct the corresponding GRNs. In both cases presented in this figure the red lines correspond to the test composite scores of the ENFRN structures using the alpha dataset while the blue when using the cdc28 subset.
Table 12: Comparison in terms of accuracy and computational time of the proposed method against 3 other methods. We also check against different parameter setups for ENFRN. For the results of this table we have used alpha subset as testing dataset.

| Modeling Approach | Particles used in BPSO (structure simplification) | Particles used in PSO (parameters fine-tuning) | Avg of Composite Score | True Positives | True Positives (Intermediate gene) | False Positives | Time (mins) |
|-------------------|--------------------------------------------------|-----------------------------------------------|------------------------|----------------|-----------------------------------|----------------|------------|
| ENFRN             | 5                                                | 5                                             | 0.456                  | 15             | 3                                 | 3              | 6          |
|                   | 10                                               | 10                                            | 0.412                  | 12             | 5                                 | 2              | 9          |
|                   | 15                                               | 15                                            | 0.390                  | 12             | 4                                 | 2              | 12         |
| RSONFIN           | -                                                | -                                             | -                      | 5              | 5                                 | 6              | 22         |
| Bayesian Network  | -                                                | -                                             | -                      | 3              | 4                                 | 7              | 29         |
| Dynamic Bayesian Network | -                                              | -                                             | -                      | 5              | 4                                 | 4              | 31         |

Figure 7: Time needed for the 1st phase of the proposed ENFRN-based methodology to roughly select the best sets of regulators for all genes in a specific dataset. The x-axis represents the subsets of genes selected for reconstructing the corresponding networks ranging from 5 to 150 genes with a step of increase of 5. As we can see, despite the fact that the method follows an exponential growth in the time needed, it took less than 2.5 minutes to finish the coarse reconstruction of a subset containing 150 genes.