A regulatory similarity measure using the location information of transcription factor binding sites in *Saccharomyces cerevisiae*

Wei-Sheng Wu, Ming-Liang Wei, Chia-Ming Yeh, Darby Tien-Hao Chang*

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**Abstract**

**Background:** Defining a measure for regulatory similarity (RS) of two genes is an important step toward identifying co-regulated genes. To date, transcription factor binding sites (TFBSs) have been widely used to measure the RS of two genes because transcription factors (TFs) binding to TFBSs in promoters is the most crucial and well understood step in gene regulation. However, existing TFBS-based RS measures consider the relation of a TFBS to a gene as a Boolean (either ‘presence’ or ‘absence’) without utilizing the information of TFBS locations in promoters.

**Results:** Functional TFBSs of many TFs in yeast are known to have a strong positional preference to occur in a small region in the promoters. This biological knowledge prompts us to develop a novel RS measure that exploits the TFBS location information. The performances of different RS measures are evaluated by the fraction of gene pairs that are co-regulated (validated by literature evidence) by at least one common TF under different RS scores. The experimental results show that the proposed RS measure is the best co-regulation indicator among the six compared RS measures. In addition, the co-regulated genes identified by the proposed RS measure are also shown to be able to benefit three co-regulation-based applications: detecting gene co-function, gene co-expression and protein-protein interactions.

**Conclusions:** The proposed RS measure provides a good indicator for gene co-regulation. Besides, its good performance reveals the importance of the location information in TFBS-based RS measures.

**Background**

Identification of co-regulated genes are helpful for solving many biological problems such as unraveling the underlying molecular mechanisms of specific cellular functions, identifying functionally related proteins and dissecting the gene regulatory networks [1-3]. The first step toward identifying co-regulated genes is to define the regulatory similarity (i.e., the degree of co-regulation) of two genes. Gene regulation is a complex process, which involves various mechanisms: transcription factors (TFs) binding, miRNAs binding, epigenetic modifications, etc. Nowadays, various data related to these mechanisms, such as TF binding sites, miRNA binding sites and histone modification patterns, are available for gene regulation study. Among them, TF binding sites (TFBSs) have been the most widely used data. This is because that TFs binding to TFBSs in promoters is the most crucial and well understood step in gene regulation.

To date, many studies have been proposed to use TFBS data to measure the regulatory similarity (RS) of two genes [4-8]. However, existing TFBS-based RS measures consider the relation of a TFBS to a gene as a Boolean (either ‘presence’ or ‘absence’) without utilizing the information of TFBS locations. In yeast and human, functional TFBSs of many TFs are known to have a strong positional preference to occur in a small region in the promoters [9,10]. This biological knowledge prompts us to develop a novel
RS measure that exploits the TFBS location information. Following Allocco et al.’s approach [11], the performances of different RS measures are evaluated by the fraction of gene pairs that are co-regulated (validated by the literature evidence deposited in the YEASTRACT database [12]) by at least one common TF under different RS scores. The experimental results show that the proposed RS measure was the best co-regulation indicator among the six compared RS measures. In addition, the co-regulated genes identified by the proposed RS measure are also shown to be able to benefit three co-regulation-based applications: detecting gene co-function, gene co-expression and protein-protein interactions.

Methods
This study proposes a novel RS measure using the TFBS location information. This section first describes the datasets used in this study and five existing TFBS-based RS measures followed by the proposed RS measure.

Datasets
Following previous studies in the literature, the promoter of a yeast gene in this study is defined as the intergenic region between this gene and its nearest non-overlapped upstream gene [13-18]. The genomic locations of the start and stop codons of 6604 genes of *Saccharomyces cerevisiae* (the budding yeast) were retrieved from Nagalakshmi et al.’s work [19]. The genomic locations of 422576 TFBSs of 163 yeast TFs were collected from the SwissRegulon database [20], which deposited high-quality TFBS datasets predicted using Bayesian probabilistic analysis. Users can choose different posterior probability cutoffs to control the quality of the retrieved TFBSs. This study adopted a moderate cutoff of 0.5 and included a section to discuss the influence of the TFBS quality to the proposed RS measure.

Existing TFBS-based RS measures
Table 1 lists five existing TFBS-based RS measures of two genes, $a$ and $b$. The first three RS measures do not consider the copies of TFBSs (namely a TF having multiple TFBSs is identical to that having one TFBS), while the last two do. In the context, TFs whose TFBS exist in the promoter of $a$ and $b$ are denoted as $TF_a$ and $TF_b$, respectively. TFs that have TFBSs in the promoters of both $a$ and $b$, (i.e. $TF_a \cap TF_b$) are named as common TFs. In the first group of RS measures, Garten et al. adopted the Jaccard index to define the similarity of promoter organization between two genes [5]. This index calculates the RS as the size ratio of the intersection to the union of $TF_a$ and $TF_b$. Shalgi et al. proposed a variant of Eq. (2) by replacing the denominator with the smaller size of $TF_a$ and $TF_b$ [6]. In the second group of RS measures, Park et al. used the proportion of TFBSs in common as the RS of two genes and introduced a penalty term for TFBSs appearing in only one gene’s promoter [7]. Van Helden adopted the Poisson distribution to

### Table 1 Five existing TFBS-based RS measures

| RS measure | Equation |
|------------|----------|
| Garten et al. | $-\log\left(\sum_{x=0}^{m} \frac{\binom{m}{x} \binom{N-m}{n-x}}{\binom{N}{n}}\right)$ Eq. (1) |
| Veerla and Höglund | $\frac{|TF_a \cap TF_b|}{|TF_a \cup TF_b|}$ Eq. (2) |
| Shalgi et al. | $\frac{|TF_a \cap TF_b|}{\min(|TF_a|, |TF_b|)}$ Eq. (3) |
| Park et al. | $S = \sum_{j=1}^{I} \sum_{i} \left(\frac{1}{2(N_{1i} + N_{2i})}\right)^{-1/2}$ Eq. (4) |
| van Helden | $M^{ab} = S^{ab} - \gamma L^{ab} + \beta$ Eq. (5) |

RS measures of two genes, $a$ and $b$. $TF_a$ and $TF_b$ represent the TFs whose TFBSs exist in the promoter of $a$ and $b$, respectively. In Eq. (1), $N$ is the number of TFs whose binding sites are in the collected TFBS data, $m=|TF_a|$, $n=|TF_b|$ and $k=|TF_a \cap TF_b|$. Equations (4) and (5) only show the final equations of the two works. The equation details can be found in the original manuscripts [7,8].
define the RS of two gene as the difference of the similarity score (1-the p-value of the observed TFBSs in common) and the dissimilarity score (the difference between the p-values of the observed TFBSs in a and in b) [8].

The proposed RS measure
Equations (1)-(5) consider the relation of a TFBS to a gene as a Boolean (either ‘presence’ or ‘absence’) without utilizing the information of TFBS locations in the promoters. The biological knowledge that the biological relevance of TFBSs is highly related to their locations in the promoters [9,10] motivates us to introduce the TFBS location information into the RS measure as follows:

$$\frac{1}{|TF_a \cap TF_b|} \sum_{i \in TF_a \cap TF_b} \frac{L - d_i}{L}, \text{ Eq. (6)}$$

where $L$ is the longer promoter length of genes $a$ and $b$, $i$ is the $i$-th common TF that has TFBSs in the promoters of both $a$ and $b$, and $d_i$ is the smallest distance between any two $i$-th common TF’s TFBSs in different promoters. In this context, $d_i$ is called TFBS offset distance. A schematic explanation of Eq. (6) is shown in Figure 1, where TFBSs have different shapes for different TFs and have different colors for different genes where they locate. The two promoters of $a$ and $b$ are aligned by the start codons (Gene View). To compute $d_i$, only the TFBSs of the $i$-th common TF are used and those of other TFs are ignored (TF View). In Figure 1, a small $d_i$, which leads to a high RS, indicates that the TFBSs of the $i$-th common TF in the two promoters are in a similar region.

Results and discussion
Small TFBS offset distances imply high regulatory similarity
This study is motivated by the biological knowledge that functional TFBSs of many TFs in yeast are known to have a strong positional preference in the promoters [9]. Because the critical regions in the promoters that make TFBSs functional are unknown, Eq. (6) is actually based on a derived hypothesis: if the offset distance of two TFBSs of a common TF in two genes’ promoters is small, the two TFBSs are prone to co-present in the critical regions and therefore be co-functional. To investigate the practicability of the above hypothesis, a relation analysis of the co-functionality and the TFBS offset distance was conducted as follows. As shown in Figure 1, a TFBS offset distance can be computed given a TF $t$ and two genes $a$ and $b$, denoted as a $<t, a, b>$ tuple. In this analysis, the co-functionality related to a TFBS offset distance was defined as the ratio of tuples in which the literature evidences collected by the YEASTRACT database [12] showed that TF $t$ regulates both $a$ and $b$ to all tuples. The detailed steps are listed below:

- For a TF $t$, all gene pairs $<a, b>$ whose promoters have the TFBS of $t$ were collected.
- The TFBS offset distance (as $d_i$ in Figure 1) of $t$ relative to $<a, b>$ was calculated.
- A tuple $<t, a, b>$ was stored in the bucket of the TFBS offset distance, $B_d$, where $d$ is the TFBS offset distance of $<t, a, b>$.
- After repeating 1-3 for all TFs, each bucket contains all tuples having the same TFBS offset distance.
- Finally, the relation of $d$ and the ratio of tuples in the bucket $B_d$ in which the literature evidences showed that TF $t$ regulates both $a$ and $b$ to all tuples was plotted.

The results are shown in Figure 2, where each point is a bucket, the $x$-axis is the TFBS offset distance, while $y$-axis is the ratio of tuples in which the literature evidences showed that TF $t$ regulates both $a$ and $b$ to all tuples. Figure 2 shows an obvious linear relation ($R^2 = 0.8106$), which suggest that the above hypothesis is practically usable. Reviewing Eq. (6), it implements this concept by incorporating $d_i$, where a common TF which has a smaller TFBS offset distance ($d_i$) has a larger value of $\frac{L - d_i}{L}$.

The proposed RS measure is a good co-regulation indicator
Following Allocco et al.’s approach [11], this study evaluated TFBS based RS measures by the fraction of gene
pairs that are co-regulated (validated by the literature evidence) by at least one common TF under different RS scores. From the 6604 yeast genes retrieved from Nagalakshmi et al.’s work [19], 359 genes having no TFBSs were excluded. The remaining 6245 genes formed 19496890 gene pairs, where 1443 head-to-head gene pairs (both genes in such a pair share the same promoter) were further excluded. Finally, the remaining 19495447 gene pairs were used as the evaluation dataset. Figure 3 shows the results of Eqs. (1-6) on the evaluation dataset. In Figure 3, the x-axis is the RS score obtained by different RS measures and the y-axis is the fraction of gene pairs that are co-regulated (validated by the literature evidence) by at least one common TF to all gene pairs under the corresponding RS scores.

The results show that the proposed RS score is highly correlated to the likelihood of a gene pair to be co-regulated by at least one common TF. The plot of the proposed RS measure (Figure 3a) is increasing and smooth at most regions except the few points at left. It achieved a significantly higher R² (0.963) of Spearman rank correlation than random expectation with p-value less than 0.001. In comparison with other RS measures, the R² of the proposed measure is significantly higher than those of other existing RS measures (see Table 2). Since the unique feature of the proposed RS measure is introducing TFBS location information, this shows that TFBS location information is useful in calculating regulatory similarity between two genes. The previous section showed the underlying hypothesis as well as a numerical evidence. The results in this section, furthermore, show that the implementation of Eq. (6) of the hypothesis works. Although the implementation of Eq. (6) may incorrectly increase the weights of TFBSs co-present in the non-critical regions, it effectively decreases the weights of those present in the critical region of one gene but in a non-critical region of the other gene.

**The effects of TFBS qualities**

The SwissRegulon database [20], of which the TFBS data were used in this study, provides users a parameter of posterior probability to control the quality of the obtained TFBSs. Actually most resources of TFBS locations provide parameters such as ChIP-chip p-value and phylogenetic conservation and let users to choose the most appropriate values for their applications [13,17,21]. This section aims to figure out whether the TFBS quality affects the performance of the proposed RS measure and, if it does affect, what TFBS qualities are suggested.

Figure 4 shows the results of the proposed RS measures using different SwissRegulon posterior probability cutoffs. The obvious turn at the region of 0.00~0.05 of the curves corresponding to high cutoffs (0.8 and 0.9) reveals that the proposed RS measure (x-axis) were badly correlated to the likelihood of a gene pair to be co-regulated by at least one common TF (y-axis). The curves of the next two lower cutoffs (0.7 and 0.6) were smoother but still had a small peak around x = 0.15. As the cutoff dropped, the correlation of the x-axis and y-axis was getting stronger. These results suggest a strange conclusion: the proposed RS measure requires TFBS quality worse than a threshold. This conclusion could be explained by the TFBS quantity (Table 3). It is reasonable that the quality cutoff also affected the quantity. The TFBS quantity of cutoff 0.1 was about three times to that of cutoff 0.7 and ten times to that of cutoff 0.9. The results suggest that, instead of TFBS quality, the proposed RS measure was more sensitive to the drastic change of TFBS quantity. With enough TFBS quantity, the proposed RS measure is robust to current TFBS data, even using the one with the lowest quality (cutoff 0.1).

**Case study**

This section uses a case (yeast CCT8) to explain the performance advantage of the proposed RS measure. CCT8 is a subunit of the cytosolic chaperonin Cct ring complex. In this case study, yeast CCT8 was of interest and its co-regulated genes were wanted. For this purpose, the RSs of all yeast genes to CCT8 were calculated and the 30 highest ranked genes were considered as co-regulated gene candidates of CCT8 (Table 4). To dig in the uniqueness of the proposed RS measure, we focused on a candidate, RPN8, which is only identified by the proposed RS measure but not identified by the other five compared RS measures. We further dug into which genes were ranked before RPN8 (therefore pushed it out the candidate list) by the other RS measures and found an interesting opponent gene, RSC1, against RPN8.

Table 5 shows the rank orders of the two genes (RPN8 and RSC1) among all yeast genes by the similarity to CCT8 using different RS measures. In this table, the proposed RS measures gave a better rank of RPN8 (#29) than
that of RSCI (#117), but all the other five RS measures gave a reverse rank order. To further investigate the details, the promoters of CCT8, RPN8 and RSCI were plotted (Figure 5). Figure 5a depicts the aligned promoters of CCT8 and RPN8; while Figure 5b depicts the aligned promoter of CCT8 and RSCI. The number of common TFs of CCT8 and RPN8 is three, and the number of common TFs of CCT8 and RSCI is five. This is why the other TFBS-based RS measures give a better rank of RSCI than that of RPN8. However, two of the three common TFs of CCT8 and RPN8 has small TFBS offset distance (Rpn4 and Abf1) and only one of the five common TFs of CCT8 and RPN8 has small TFBS offset distance (Abf1). Since the proposed RS measure is the only one that

**Figure 3 Comparison of six regulatory similarity measures**. This figure is plotted as follows. First, a subset of one million samples was randomly selected from the evaluation dataset of 19495447 gene pairs. Second, the scores of the selected gene pairs are calculated. Third, the correlation plot of one subset is generated. Each point represents 2% of gene pairs (each figure contains 50 points) in that subset. In a correlation plot, x and y are the average RS score and the fraction of gene pairs that are co-regulated (validated by the literature evidence deposited in the YEASTRACT database) by at least one common TF, respectively. The gene pairs were sorted by the RS score. For example, the rightest point represents the 2% gene pairs of the highest RS scores. Finally, the three steps are repeated 100 times and this figure shows an average plot of 100 correlation plots. The dashed line indicates a random predictor in which RS scores are randomly assigned.
Table 2 Significance of performance difference of the proposed RS measure against five methods

| RS measure           | P-value   |
|----------------------|-----------|
| van Helden           | 5.36 × 10^{-24} |
| Veerla and Höglund   | 3.23 × 10^{-23} |
| Garten et. al.       | 4.82 × 10^{-23} |
| Park et. al.         | 4.88 × 10^{-23} |
| Shalgi et. al.       | 8.04 × 10^{-137} |

P-values are calculated by one-tailed t-test.

To justify the correctness of the rank order, the biological relevance of common TFs were analyzed. In this study, a TF is defined biologically relevant to a gene if the literature evidences obtained from the YEASTRACT database show that the TF regulates the gene. In Figure 5, all TFs with small TFBS offset distances are biologically relevant to both target genes (Rpn4 and Abf1 to both CCT8 and RPN8 in (a) and Abf1 to both CCT8 and RSC1 in (b)). Furthermore, all the other TFs, which have large TFBS offset distances, are not simultaneously relevant to both downstream genes. This suggests the correctness of the proposed RS measure as well as the importance of incorporating the information of TFBS locations.

Good RS measure benefits co-regulation-based applications

Co-regulated genes are considered to influence many biological behaviors and co-regulation measures have been used in various applications [22,23]. The section “The proposed RS measure is a good co-regulation indicator” shows that the proposed RS is a good co-regulation index over the five competitors. This section discusses whether this leads to a better result in three co-regulation-based applications: detecting gene co-function, gene co-expression and protein-protein interactions.

In this study, the scenario of detecting gene co-function, gene co-expression and protein-protein interactions using gene co-regulation was designed as follows. First, users have a target gene of interest. The RS score of the target gene against each gene in the genome is calculated. The n genes with the highest RSs are called the regulatory neighborhood (RN) to the target gene and n is called the neighborhood size. Then the degree of co-function of the RN is evaluated using the functional enrichment score proposed by Reimand et al. [24], denoted as FES in this study. In FES, genes are considered to perform similar biological functions if they have similar Gene Ontology (GO) terms [25]. The degree of co-expression of the RN is evaluated by the co-expression score proposed by Yang and Wu [26], denoted as CES in this study. CES is the average of the pairwise expression correlations in the RN. The degree of protein-protein interactions of the RN is evaluated by the interaction enrichment score proposed by Reimand et al. [24], denoted as IES in this study. IES measures the tendency of forming protein complex modules of a RN.

The results of the proposed RS measure and the five existing RS measures in the three applications are shown in Figure 6 and Table 6. The proposed RS measure achieved the highest performance among all the compared RS measures in all applications and all neighborhood sizes. In all three applications, the RS measures of van Helden, Veerla and Höglund and Garten et al. had similar performance and were the second best group.
Table 4 Co-regulated genes of CCT8 identified by the proposed RS measure

| Gene list                                                                 | Uniqueness |
|---------------------------------------------------------------------------|------------|
| RPN8, THI12, GTF1, GBP2, NOP7, YOR262W, NUP84, MDM32, TMA108, NUP85, URB2, MSO1 | 0          |
| THI8, PRE8, SEC65, ISN1                                                  | 1          |
| RCF1, MRPL16, TIF1, RPN3, CYM1, YGL010W, UBA7, RPA12, YNL144W-A, SCL1, EMC4 | 2          |
| CSH1, YLR030W, RPL15A                                                   | 3          |

1Number of RS measures among the five compared ones (Table 1) that also identified the genes. For example, the uniqueness of RPN8 is 0, indicating that it is only identified by the proposed RS measure but not identified by the five compared ones.

Table 5 Ranks of RPN8 and RSC1 against CCT8

| RS measure          | RPN8¹ | Order² | RSC1³ |
|---------------------|-------|--------|-------|
| This work           | 29    | <      | 117   |
| van Helden          | 3162  | >      | 244   |
| Veerla and Höglund  | 37    | >      | 31    |
| Garten et. al.      | 61    | >      | 33    |
| Park et. al.        | 126   | >      | 26    |
| Shalgi et. al.      | 402   | >      | 330   |

1Rank of the RS score of RPN8 against CCT8 among the RS scores of all yeast genes against CCT8. ²Symbol ‘<’ indicates that the RS score of RPN8 against CCT8 is higher than that of RSC1; symbol ‘>’ indicates that the RS score of RPN8 against CCT8 is lower than that of RSC1. ³Rank of the RS score of RSC1 against CCT8 among the RS scores of all yeast genes against CCT8.

Figure 5 Case study (a) The aligned promoters of CCT8 and RPN8. (b) The aligned promoter of CCT8 and RSC1. 
Figure 6 Comparison of six regulatory similarities on three applications. The x-axis is the neighborhood size of the regulatory neighborhood (RN) while the y-axis is the degree of (top) gene co-function calculated using the functional enrichment score (FES), (middle) gene co-expression calculated using the co-expression score (CES) and (bottom) protein-protein interactions using the interaction enrichment score (IES) of the RN identified by the RS measure.
Table 6 Comparison of six regulatory similarities on three applications

| RS measure                                      | FES | CES | IES | Average |
|------------------------------------------------|-----|-----|-----|---------|
| This work                                      | 1   | 1   | 1   | 1.0     |
| van Helden                                    | 2   | 2   | 2   | 2.0     |
| Veerla and Höglund                            | 3   | 4   | 3   | 3.3     |
| Garten et al.                                  | 4   | 3   | 4   | 3.7     |
| Park et al.                                    | 5   | 5   | 5   | 5.0     |
| Shalgi et al.                                  | 6   | 6   | 6   | 6.0     |

1The RS measures are ranked in terms of gene co-function (the area under curve (AUC) of Figure 6a). 2The RS measures are ranked in terms of gene co-expression (the AUC of Figure 6b). 3The RS measures are ranked in terms of protein-protein interaction (the AUC of Figure 6c). 4The average of the ranks by gene co-function, gene co-expression and protein-protein interactions.

Conclusions

This study proposed a novel measure that can compute the regulatory similarity (RS) of two genes using the location information of transcription factor binding sites. Based on the documented regulation associations between TFs and genes in the YEASTRACT database, this study has shown that the proposed RS measure is a good co-regulator indicator. Furthermore, its good performance can benefit to three co-regulation-based applications. The proposed RS measure will be helpful for unraveling the underlying molecular mechanisms of specific cellular functions and dissecting the gene regulatory networks.

Authors’ contributions

WSW and DTHC conceived the research topic, provided essential guidance, developed the algorithm and wrote the manuscript. MLW and CMY performed all the simulations. All authors read and approved the final manuscript.

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References

1. Terai G, Takagi T, Nakai K. Prediction of co-regulated genes in Bacillus subtilis on the basis of upstream elements conserved across three closely related species. Genome Bioi 2001, 2(11), research0048:0001-research0048:0012.
2. Polancki K, Rhodes J, Hill C, Zhang P, Jenkins DJ, Kiddie SJ, Jorcinin A, Beynon J, Buchanan-Wollaston V, Ott S. Wigwams: identifying gene modules co-regulated across multiple biological conditions. Bioinformatics 2014, 30(7):962-970.
3. Lin TW, Wu JW, Chang DTH. Combining phylogenetic profiling-based and machine learning-based techniques to predict functional related proteins. PLoS one 2013, 8(9):e75940.
4. Garten Y, Kaplan S, Pilpel Y. Extraction of transcription regulatory signals from genome-wide DNA-protein interaction data. Nucleic Acids Research 2003, 31(2):605-615.
5. Veerla S, Höglund M. Analysis of promoter regions of co-expressed genes identified by microarray analysis. Bioinformatics 2006, 22(11):1284.
6. Shalgi R, Lieber D, Dren M, Pilpel Y. Global and local architecture of the mammalian microRNA-transcription factor regulatory network. PLoS Computational Biology 2007, 3(7):e131.
7. Park PJ, Butte AJ, Kohane IS. Comparing expression profiles of genes with similar promoter regions. Bioinformatics 2002, 18(12):1576-1584.
8. Van Heiden J. Metrics for comparing regulatory sequences on the basis of pattern counts. Bioinformatics 2004, 20(3):399-406.
9. Hansen L, Marín-Ramírez L, Landsman D. Many sequence-specific chromatin modifying protein-binding motifs show strong positional preferences for potential regulatory regions in the Saccharomyces cerevisiae genome. Nucleic Acids Research 2010, 38(6):1772-1779.
10. Tabach Y, Brosh R, Buganim Y, Reiner A, Zuk O, Yitzhaki A, Kudritsky M, Rotter V, Domany E. Wide-scale analysis of human functional transcription factor binding reveals a strong bias towards the transcription start site. PLoS One 2007, 2(8):e807.
11. Allocco DJ, Kohane IS, Butte AJ. Quantifying the relationship between co-expression, co-regulation and gene function. BMC bioinformatics 2004, 5(118).
12. Terefeia MC, Montero P, Jain P, Tenerino S, Fernandes AR, Mira NP, Alencner M, Freitas AT, Oliveira AL, Sa-Correia I. The YEASTRACT database: a tool for the analysis of transcription regulatory associations in Saccharomyces cerevisiae. Nucleic Acids Research 2006, 34(suppl 1):D446-D451.
13. MacIsaac KD, Wang T, Gordon DB, Gifford DK, Stormo GD, Fraenkel E. An improved map of conserved regulatory sites for Saccharomyces cerevisiae. BMC Bioinformatics 2006, 7(113).
14. Lee TI, Rinaldi NJ, Robert F, Odorn DT, Bar-Joseph Z, Gerber GK, Hannett NM, Harbison CT, Thompson CM, Simon I. Transcriptional regulatory networks in Saccharomyces cerevisiae. Science 2002, 298(5594):799-804.
15. Simon I, Barnett J, Hannett N, Harbison CT, Rinaldi NJ, Volkert TL, Wynick J, Zeitlinger J, Gifford DK, Jaakkola TS. Serial regulation of transcriptional regulators in the yeast cell cycle. Cell 2001, 106(6):697-708.
16. Harbison CT, Gordon DB, Lee TI, Rinaldi NJ, MacIsaac KD, Danford TW, Hannett NM, Tagne JB, Reynolds DB, Yoo J. Transcriptional regulatory code of a eukaryotic genome. Nature 2004, 431(7004):99-104.
17. Chang DTH, Huang CY, Wu CY, Wu WS. YPA: an integrated repository of promoter features in Saccharomyces cerevisiae. Nucleic acids research 2011, 39(suppl 1):D667-D662.
18. Chang DTH, Li WS, Bai YH, Wu WS. YGA: Identifying distinct biological features between yeast gene sets. Gene 2013, 518(1):26-34.
19. Nagalakshmi U, Wang Z, Wairm K, Shou C, Raha D, Gerstein M, Snyder M. The transcriptional landscape of the yeast genome defined by RNA sequencing. Science 2008, 320(5881):1344-1349.
20. Pachikov M, Eri I, Molina N, Van Nimwegen E. SwissRegulon: a genome database of annotated regulatory sites. Nucleic Acids Research 2007, 35(suppl 1):D127-D131.
21. Tsai HK, Chou MY, Shih CH, Huang GTW, Chang TH, Li WT. MYBS: a comprehensive web server for mining transcription factor binding sites in yeast. Nucleic Acids Research 2007, 35(suppl 2):W221-W226.
22. Bhardwaj N, Lu H. Correlation between gene expression profiles and protein-protein interactions within and across genomes. Bioinformatics 2005, 21(11):2730-2738.
23. Gynensie A, Wagner U, Barkow-Oesterreicher S, Stolle E, Schlapbach R. Mining co-regulated gene profiles for the detection of functional associations in gene expression data. Bioinformatics 2007, 23(15):1927-1935.
24. Neumann JR, Vaquero-Zam J, Todde AE, Vila A, Luscombe NM. Comprehensive reanalysis of transcription factor knockout expression data in Saccharomyces cerevisiae reveals many new targets. Nucleic Acids Research 2010, 38(14):4768-4777.
25. Gene Ontology C. The gene ontology: enhancements for 2011. Nucleic Acids Research 2012, 40(D1):D559-D564.
26. Yang TH, Wu WS. Identifying biologically interpretable transcription factor knockout targets by jointly analyzing the transcription factor knockout microarray and the ChiP-chip data. BMC Systems Biology 2012, 6(1):102.

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