# Supplementary Methods

## 1 Parameter Estimation and Inference

The posterior distribution of our unknown parameters is proportional to the product of our model likelihood and our assumed prior distributions,

$$\begin{aligned} p(\mathbf{C}, \mathbf{w}, \boldsymbol{\Theta} | \mathbf{g}, \mathbf{f}, \mathbf{m}, \mathbf{b}) &\propto p(\mathbf{g}|\mathbf{f}, \mathbf{C}, \boldsymbol{\Theta}) \cdot p(\mathbf{C}|\mathbf{m}, \mathbf{b}, \mathbf{w}) \cdot p(\mathbf{w}) \cdot p(\boldsymbol{\alpha}) \cdot p(\boldsymbol{\beta}) \cdot p(\sigma^2) \\ &\propto \prod_{i=1}^{N}\prod_{t=1}^{T}(2\pi\sigma^2)^{-1/2} \exp\left[\frac{-1}{2\sigma^2}\left(g_{it} - \alpha_i - \sum_{j=1}^{J}\beta_j X_{ijt}\right)^2\right] \\ &\quad \cdot \prod_{i=1}^{N}\prod_{j=1}^{J}\left[b_{ij}^{C_{ij}}(1-b_{ij})^{1-C_{ij}}\right]^{w_j} \cdot \left[m_{ij}^{C_{ij}}(1-m_{ij})^{1-C_{ij}}\right]^{1-w_j} \\ &\quad \cdot \prod_{i=1}^{N}(\tau_\alpha^2)^{-1/2}\exp\left[\frac{-1}{2\tau_\alpha^2}\alpha_i^2\right] \cdot \prod_{j=1}^{J}(\tau_\beta^2)^{-1/2}\exp\left[\frac{-1}{2\tau_\beta^2}\beta_j^2\right] \cdot (\sigma^2)^{-2}\exp\left[\frac{-1}{2\sigma^2}\right] \end{aligned}$$

where $X_{ijt} = C_{ij} f_{jt}$. We estimate all unknown parameters by Gibbs sampling, ie. by iteratively estimating one set of parameters given all other parameters. Specifically, we iterate between

1. Estimating $\boldsymbol{\Theta}$ given $\mathbf{C}, \mathbf{w}$ and data $\mathbf{g}, \mathbf{f}, \mathbf{b}, \mathbf{m}$
2. Estimating $\mathbf{C}$ given $\mathbf{w}, \boldsymbol{\Theta}$ and data $\mathbf{g}, \mathbf{f}, \mathbf{b}, \mathbf{m}$
3. Estimating $\mathbf{w}$ given $\mathbf{C}, \boldsymbol{\Theta}$ and data $\mathbf{g}, \mathbf{f}, \mathbf{b}, \mathbf{m}$

The details of these steps are given in the following sections. The result of this Gibbs sampling algorithm is a set of values for each parameter from the posterior distribution given above. In this study, we use these posterior parameter values for inference in two different ways. First, the parameter values for each $C_{ij}$ are used to define whether gene $i$ is actually regulated by TF $j$ according to our model: if the majority of parameter values for $C_{ij}$ are $C_{ij} = 1$ (as opposed to $C_{ij} = 0$), then we claim that gene $i$ is regulated by TF $j$. This gene is then placed in the **C+** group for TF $j$. Secondly, we use the parameter values for our linear effects $\boldsymbol{\beta}$ and interaction effects $\boldsymbol{\gamma}$ to form 95% posterior intervals for each parameter $\beta_j$ and $\gamma_{jk}$ by excluding the most extreme 2.5% of the parameter draws in either direction. If the posterior interval for a particular $\beta_j$ does not contain zero, we conclude that there is significant linear effect for TF $j$. Similarly, if the posterior interval for a particular $\gamma_{jk}$ does not contain zero, we concluded that there is a significant interaction effect between the TFs $j$ and $k$.

## 2 Algorithm Step 1: Estimating linear model parameters $\boldsymbol{\Theta}$

The regulation matrix $\mathbf{C}$ is assumed known during this step, so we do not need to use our prior data $\mathbf{b}, \mathbf{m}$ or the current values of $\mathbf{w}$. We use $\mathbf{C}$ to construct the variables $\mathbf{X}$ where$X_{ijt} = C_{ij} f_{jt}$. The linear model parameters $\boldsymbol{\Theta}$ are then separately estimated by the following iterative strategy.

a. **Estimate $\alpha_i$ given $\boldsymbol{\beta}, \sigma^2$ and data ($g$'s and $X$'s):**
Since each intercept $\alpha_i$ is independent from the other $\alpha$'s, they can be separately sampled,

$$\begin{aligned} p(\alpha_i|\boldsymbol{\beta}, \sigma^2, \mathbf{g}, \mathbf{X}) &\propto \exp\left[\frac{-1}{2\sigma^2}\sum_{t=1}^{T}\left(g_{it} - \alpha_i - \sum_{j=1}^{J}\beta_j X_{ijt}\right)^2\right] \cdot \exp\left[\frac{-1}{2\tau_\alpha^2}\alpha_i^2\right] \\ &\propto \exp\left[\frac{-1}{2\nu_\alpha}\left(\alpha_i - \frac{\nu_\alpha}{\sigma^2}\cdot\sum_{t=1}^{T}Y_t\right)^2\right] \end{aligned}$$

where $Y_t = g_{it} - \sum_{j=1}^{J} \beta_j X_{ijt}$ and $\nu_\alpha = (T/\sigma^2 + 1/\tau_\alpha^2)^{-1}$. This distribution implies that

$$\alpha_i \sim \text{Normal}\left(\frac{\nu_\alpha}{\sigma^2} \cdot \sum_{t=1}^{T} Y_t \ , \ \nu_\alpha\right)$$

We can make our prior distribution for each $\alpha_i$ to be non-informative by making $\tau_\alpha$ very large (in this study, 10000) relative to the contribution of the likelihood to the variance ($\sigma^2/T$).

b. **Estimate $\beta_j$ given $\boldsymbol{\alpha}, \sigma^2$ and data ($g$'s and $X$'s).**
Note that in the step below, we have combined our notation for interaction coefficients $\gamma_{jk}$ and linear coefficients $\beta_j$ into a single vector of parameters $\boldsymbol{\beta}$. These coefficients $\beta_j$ are not independent from each other, and so must be iteratively sampled themselves:

$$\begin{aligned} p(\beta_j|\boldsymbol{\alpha}, \sigma^2, \mathbf{g}, \mathbf{X}) &\propto \exp\left[\frac{-1}{2\sigma^2}\sum_{i=1}^{N}\sum_{t=1}^{T}\left(g_{it} - \alpha_i - \sum_{j'=1}^{J}\beta_{j'}X_{ij't}\right)^2\right] \cdot \exp\left[\frac{-1}{2\tau_\beta^2}\beta_j^2\right] \\ &\propto \exp\left[\frac{-1}{2\sigma^2}\sum_{i=1}^{N}\sum_{t=1}^{T}\left(V_{it} - \beta_j X_{ijt}\right)^2\right] \cdot \exp\left[\frac{-1}{2\tau_\beta^2}\beta_j^2\right] \end{aligned}$$

where $V_{it} = g_{it} - \alpha_i - \sum_{j' \neq j} \beta_{j'} X_{ij't}$, which reduces further to

$$p(\beta_j|\boldsymbol{\alpha}, \sigma^2, \mathbf{g}, \mathbf{X}) \propto \exp\left[\frac{-1}{2\nu_\beta}\left(\beta_j - \frac{\nu_\beta}{\sigma^2} \cdot T_{VX}\right)^2\right]$$

where $\nu_\beta = (T_{XX}/\sigma^2 + 1/\tau_\beta^2)^{-1}$, $T_{XX} = \sum_{i=1}^{N}\sum_{t=1}^{T} X_{ijt}^2$ and $T_{VX} = \sum_{i=1}^{N}\sum_{t=1}^{T} V_{it}X_{ijt}$.
This distribution implies that

$$\beta_j \sim \text{Normal}\left(\frac{\nu_\beta}{\sigma^2} \cdot T_{VX} \ , \ \nu_\beta\right)$$

Note that the distribution of $\beta_j$ depends on the values of the other $\beta_{j'}$'s, so we must sample the $\beta_j$'s one at a time given the current values of the other $\beta_{j'}$'s. We can make our prior distribution for each $\beta_j$ to be non-informative by making $\tau_\beta$ very large (in this study, 10000) relative to the contribution of the likelihood to the variance ($\sigma^2/T_{XX}$).

c. **Estimate $\sigma^2$ given $\boldsymbol{\beta}, \boldsymbol{\alpha}$ and data ($g$'s and $X$'s).**
For the residual variance $\sigma^2$, we have the following conditional distribution

$$\begin{aligned} p(\sigma^2|\boldsymbol{\alpha}, \boldsymbol{\beta}, \mathbf{g}, \mathbf{X}) &\propto (\sigma^2)^{-\left(\frac{TN}{2}+2\right)} \cdot \exp\left[\frac{-1}{2\sigma^2}\sum_{i=1}^{N}\sum_{t=1}^{T}\left(g_{it} - \alpha_i - \sum_{j=1}^{J}\beta_j X_{ijt}\right)^2\right] \cdot \exp\left(\frac{-1}{2\sigma^2}\right) \\ &\propto (\sigma^2)^{-\left(\frac{TN+2}{2}+1\right)} \cdot \exp\left[\frac{-1}{2\sigma^2}\left(V_\sigma + 1\right)\right] \end{aligned}$$

where $V_\sigma = \sum_{i=1}^{N}\sum_{t=1}^{T}(g_{it} - \alpha_i - \sum_{j=1}^{J}\beta_j X_{ijt})^2$. The above calculations use a $\chi_\nu^2$ prior distribution for $\sigma$ with hyper-parameter $\nu = 2$. We see that the influence of this prior is very small on the posterior distribution for $\sigma^2$, which is a scaled-inverse $\chi^2$ distribution with degrees of freedom parameter $TN + 2$ and scale parameter $s^2 = (V_\alpha + 1)/(TN + 2)$.

## 3 Algorithm Step 2: Estimating regulation matrix C

We are assuming that both our linear model parameters $\mathbf{\Theta}$ and our weights $\mathbf{w}$ are known for this step of the algorithm. When estimating a new value for each $C_{ij}$, we also can condition on $\mathbf{C}'$, which is all the other $C_{i'j'}$ values in $\mathbf{C}$ ($i' \neq i$ and $j' \neq j$). This gives us the following conditional distribution for $C_{ij}$:

$$p(C_{ij}|\mathbf{\Theta}, \mathbf{w}, \mathbf{C}', \mathbf{g}, \mathbf{f}, \mathbf{b}, \mathbf{m}) \propto \exp\left[\frac{-1}{2\sigma^2}\sum_{t=1}^{T}\left(g_{it} - \alpha_i - \sum_{j=1}^{J}\beta_j C_{ij} f_{jt}\right)^2\right] \cdot \left[b_{ij}^{C_{ij}}(1-b_{ij})^{1-C_{ij}}\right]^{w_j} \cdot \left[m_{ij}^{C_{ij}}(1-m_{ij})^{1-C_{ij}}\right]^{1-w_j} \quad (1)$$

Let $Z_1$ be the value of equation (1) when $C_{ij} = 1$ and $Z_0$ be the value of equation (1) when $C_{ij} = 0$. We sample a new value of $C_{ij}$ as follows:

$$C_{ij} = \begin{cases} 1 & \text{with probability } Z_1^\star \\ 0 & \text{with probability } Z_0^\star \end{cases}$$

where $Z_i^\star = Z_i/(Z_1 + Z_0)$. Moreover, to understand the contribution from expression data, we can design COGRIM to update the indicator $C_{ij}$ without the ChIP binding and motif priors ($b_{ij}$ and $m_{ij}$).

## 4 Algorithm Step 3: Estimating prior weights w

We are assuming that the regulation matrix $\mathbf{C}$ is known for this step of the algorithm, so we do not need to use any of the expression data , $\mathbf{g}$ or linear model parameters $\mathbf{\Theta}$ at this point. For each TF $j$, we need to estimate a new weight $w_j$ based on the following distribution:

$$p(w_j|\mathbf{C}, b_{ij}, m_{ij}) \propto \left[\prod_{i=1}^{n}(b_{ij})^{C_{ij}}(1-b_{ij})^{1-C_{ij}}\right]^{w_j} \cdot \left[\prod_{i=1}^{n}(m_{ij})^{C_{ij}}(1-m_{ij})^{1-C_{ij}}\right]^{1-w_j} \quad (2)$$

Note that there is also a normalizing constant present in (2) that is also a function of $w_j$, which comes from the integration of $p(w_j, \mathbf{C}_j|\mathbf{b}, \mathbf{m})$ over all possible values of $\mathbf{C}_j$. There is no built-in function for sampling a value from equation (2), but instead we can use *grid sampling*, as follows:

1. Set up a grid of $n$ possible $w_j$ values: $\mathbf{z} = (z_1 = 0.01, z_2 = 0.02, \ldots, z_n = 0.99)$
2. Evaluate equation (2) for each of these grid values. In other words, calculate
$$p_i = p(z_i|\mathbf{C}, b_{ij}, m_{ij})$$
3. Normalize the probabilities for each grid value: $p_i^\star = p_i/\sum_i p_i$
4. Set $w_j = z_i$ with probability $p_i^\star$

## 5 Evaluating Convergence

Multiple chains of our Gibbs sampling algorithm were run from different starting points. We monitored the convergence based on the within and between variance ratio $\hat{R}$ [34], which converges towards 1 as the multiple chains converge towards each other. The maximum $\hat{R}$ values (across different parameter sets) after 5000 iterations are shown in the following table for the three applications to Yeast, C/EBP-$\beta$ and SRF. We concluded, based on these $\hat{R}$ values, that our Gibbs sampler chains had converged after 5000 iterations in each application. We also examined the autocorrelation function of the sampled draws. We observed a rapid decline in the autocorrelation for increasing lags which indicates that the sampler does not have a substantively high autocorrelation(data not shown).

| | Yeast | C/EBP-$\beta$ | SRF |
|---|---|---|---|
| $\hat{R}(\sigma^2)$ | 1.001 | 1.0002 | 1.0004 |
| $\max_i \hat{R}(\alpha_i)$ | 1.026 | 1.011 | 1.008 |
| $\max_j \hat{R}(\beta_j)$ | 1.014 | 1.005 | 1.002 |
| $\max_j \hat{R}(w_j)$ | | 1.007 | |

## 6 Permutation evaluation of the sensitivity

To understand the classification sensitivity on priors and posterior thresholds, we can employ a permutation scheme to make sure that our threshold of 0.5 is reasonable. Prior data sources $b_{ij}$ obtained from ChIP binding data can be randomly permuted and then implemented in COGRIM to be compared with our results obtained using our actual non-permuted priors. This comparison can help us understand the sensitivity of our results to both prior information and posterior thresholds. As an example, we conducted this permutation analysis on a dataset for the HAP4 transcription factor in Yeast. The comparisons showed that (data not shown) (1) inference based on permuted prior information is much more sensitive to different posterior cutoffs than our actual results and (2) both the data in our prior distributions and the likelihood of our expression data are contributing substantially to our inferred target genes.

## 7 Converting Binding p-values into Binding Probabilities

The results produced by a typical ChIP binding experiment for TF $j$ is a set of measures $Y_i$ for the enrichment of each gene $i$ for that TF $j$ (often these measures are averages calculated over several repetitions of the experiment). These measures are typically standardized, $X_i = (Y_i - \overline{Y})/s_Y$, to have a common mean and standard deviation. For each $X_i$, a significance test is performed against a null hypothesis of no enrichment, giving a p-value $p_i$ for each gene that is calculated using a standard normal or a t distribution. These p-values can not be directly interpreted as the probability $b_i = \mathrm{P}(\mathrm{TF}\ j\ \mathrm{binds\ gene}\ i)$, so we use the following procedure to convert $p_i$ into binding probabilities $b_i$ (Since $b_{ij}$ is calculated for each TF $j$ independently, we here just use $i$ notation instead of $ij$ for simplicity).

We first convert the p-values $p_i$ back to their corresponding standardized enrichment measures $X_i$ using the inverse-CDF for the standard normal distribution. The distribution of these enrichment measures $X_i$ should be a mixture of two different groups: a large group of unenriched genes that should be centered at $X = 0$ and a smaller group of genes that are truly enriched, with center $\mu > 0$. This mixture model is visually represented for the transcription factor ABF1 in the following Figure.

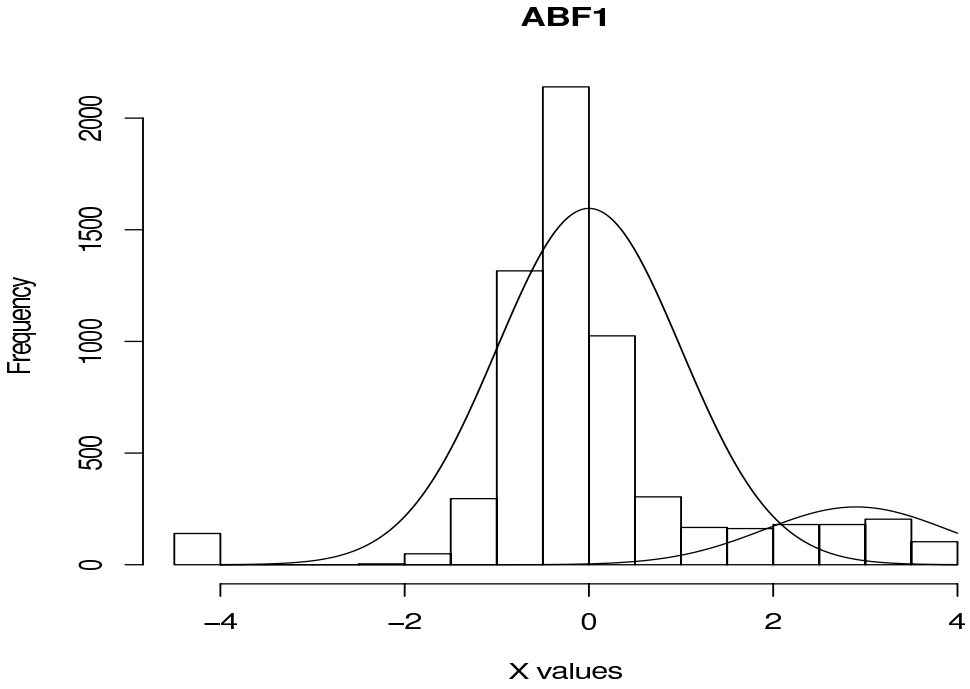
Statistically, we can model each gene with a latent variable $I_i$ that indicates whether that gene is in the enriched group ($I_i = 1$) or unenriched group ($I_i = 0$). Our desired binding probabilities for each gene are then simply $b_i = \mathrm{P}(I_i = 1)$. An EM algorithm [30] was written to simultaneously estimate the unknown parameters of our mixture model (mixing proportion and mean/variance of enriched component) as well as the $b_i = \mathrm{P}(I_i = 1)$ for each gene. This algorithm alternates between

1. estimating the unknown parameters of our mixture model given current estimates of each $b_i$:

$$\hat{\mu} = \frac{\sum_i I_i \cdot X_i}{\sum_i I_i} \qquad \hat{\tau}^2 = \frac{\sum_i I_i \cdot (X_i - \mu)^2}{\sum_i I_i} \qquad \hat{\lambda} = \frac{\sum_i I_i}{n}$$

2. estimating the unknown $b_i$'s given current estimates $\hat{\mu}$ and $\hat{\lambda}$ using Bayes rule:

$$\begin{aligned} b_i = P(I_i = 1|X_i) &= \frac{P(X_i|I_i = 1)P(I_i = 1)}{P(X_i|I_i = 1)P(I_i = 1) + P(X_i|I_i = 0)P(I_i = 0)} \\ &= \frac{\hat{\tau}^{-1} \exp(\frac{1}{2\hat{\tau}^2}(X_i - \hat{\mu})^2) \cdot \hat{\lambda}}{\hat{\tau}^{-1} \exp(\frac{1}{2\hat{\tau}^2}(X_i - \hat{\mu})^2) \cdot \hat{\lambda} + \exp(\frac{1}{2}X_i^2) \cdot (1 - \hat{\lambda})} \end{aligned}$$



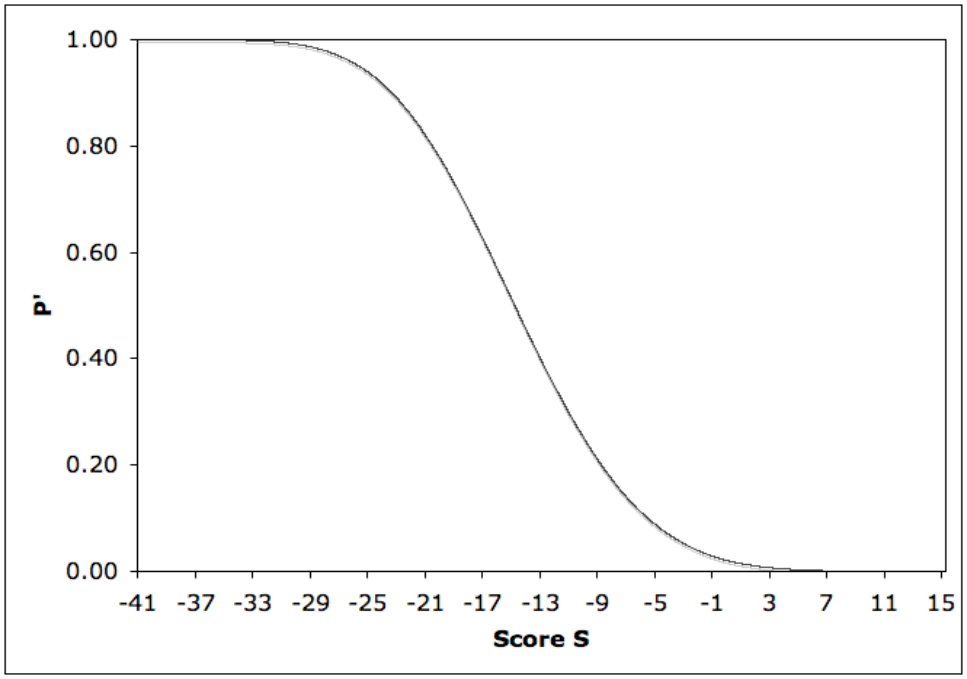

until these values converge to a fixed point. A detailed discussion of expression mixture models is given in [35]. It should be noted that our mixture model used the theoretical standard normal null distribution instead of an empirical null distribution since the use of an unrestricted mixture model (with an empirically-fitted null distribution) lead to unreasonable mixtures for several transcription factors. This procedure was repeated for each TF $j$ to generate our full set of binding probabilities $b_{ij}$. The correspondence between the number of genes we predicted as enriched based on p-values ($p_i < 0.005$) and binding probabilities ($b_i > 0.5$) is very good, with a correlation of 0.97 between the number of genes predicted across our 113 transcription factors. However, we noticed that our conversion procedure tended to be overly-conservative for genes with very low p-values. In other words, genes with $p_{ij} < 0.001$ had estimated binding probabilities that where smaller than expected, possibly due to our assumption of a standard normal null distribution. For these highly-significant genes, the binding probabilities were increased to $b_{ij} = 0.95$ to reflect our extra confidence that these genes were truly enriched in the ChIP binding experiment for TF $j$.

## 8 Calculate the Probability of TF Binding Site Occurrence

The first step in calculating a probability for a binding site occurrence for TF $j$ near to gene $i$ is to scan the genomic sequence nearby to gene $i$ for good matches to the position weight matrix (PWM) for TF $j$. The similarity between a TF PWM with width $w$ and a sequence of nucleotides $\{a_1, \ldots, a_w\}$ is defined in the equation below:

$$S(a_1, \ldots, a_w) = \sum_t \log\left(\frac{P_{t,a_t}}{B_{a_t}}\right)$$

where $P_{t,a_t}$ is the probability of observing nucleotide $a_t$ in position $t$ of the PWM, and $B_{a_t}$ is the probability of observing nucleotide $a_t$ in the background sequence. When scanning the sequence near gene $i$ for matches to the PWM of TF $j$, we only focus on the score for the best match we find, which we denote as $S_{ij}^{\max}$.




The second step of our procedure is to calculate the probability $m_{ij}$ of a binding site for TF $j$ near to gene $i$ by comparing the maximum similarity score $S_{ij}^{\max}$ to the scores $S$ that we get by applying our scanning procedure to randomly-generated $w$-mers (sequences of length $w$). More specifically, we calculate the probability of $m_{ij}$ of a binding site for TF $j$ near to gene $i$ to be the probability that we observe no score $S$ greater than $S_{ij}^{\max}$ in a randomly-generated sequence of length $L$, where $L$ is the length of our original scanned sequence near gene $i$. In other words,

$$m_{ij} = (1 - p')^{L-w+1}$$

where $L - w + 1$ is the number of possible matches to a PWM of width $w$ in a sequence of length $L$, and $p'$ is the probability that a randomly-generated $w$-mer has a score $S$ that is greater than $S_{ij}^{\max}$. As an example, for the C/EBP-$\beta$ PWM, Figure shows the value of $p'$ as a function of $S$.

TESS-DIST [24] was used for the calculation of these binding site probabilities. For short PWMs, this calculation can be done analytically by enumerating all possible $w$-mers and computing their score. However, the number of $w$-mers is $4^w$ which becomes cumbersome to enumerate as $w$ increases so TESS-DIST adopts a dynamic programming algorithm [36] to compute the approximate distribution of scores. The approximation is achieved by binning the possible scores thus reducing the total number of possible scores to a number that is linear $(O(w))$ in the length of the PWM.

## Supplementary Materials

Supplementary Table 1. Used Expression Data in Yeast

| | References |
|---|---|
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Collected Yeast expression data from public literature and database were already processed through common microarray normalization pipelines [37]. We further normalized the combined expression profiles by subtracting the mean of each profile and dividing by the standard deviation across experiments.

## Supplementary Table 2. TF pair interaction evidence

| **TF1** | **TF2** | **Evidence** |
|---|---|---|
| ACE2 | SWI4 | Stillman et al., 1994; Dohrmann et al., 1996 |
| ACE2 | SWI5 | *Doolin et al., 2001* |
| ACE2 | SKN7 | banerjee et al., 2003; Luft et al., 2001 |
| ACE2 | HSF1 | banerjee et al., 2003; Luft et al., 2001 |
| SWI4 | SWI5 | SGD |
| SWI4 | SWI6 | SGD |
| SWI4 | MBP1 | Dirick et al., 1996; Iyer et al., 2001; Horak et al., 2002 |
| SWI4 | STE12 | Baetz et al., 2001 |
| SWI6 | MBP1 | Breeden & Nasmyth, 1987; Nasmyth & Dirick, 1991; Dirick et al., 1992; Koch et al., 1993; Dirick et al., 1996; Iyer et al., 2001; Horak et al., 2002 |
| FKH1 | FKH2 | Zhu et al., 2000; Hollenhorst et al., 2000; Sun et al., 2002 |
| FKH2 | NDD1 | Pic et al., 2000; Koranda et al., Kumar et al., 2000; Sun et al., 2002 |
| FKH2 | MCM1 | Pic et al., 2000; Koranda et al., Kumar et al., 2000; Sun et al., 2002 |
| NDD1 | MCM1 | Pic et al., 2000; Koranda et al., Kumar et al., 2000; Sun et al., 2002 |
| MCM1 | STE12 | Hwang-Shumm et al., 1991; Primig et al., 1991; Errede, 1993; Kirkmann-Correia et al., 1993 |

84 TF pairs with significant effects on expression of target genes

| TF1 | TF2 | Gamma |
|---|---|---|
| ACE2 | SWI4 | 0.200536878 |
| ACE2 | SWI5 | 0.22775754 |
| ACE2 | SKN7 | 0.394727827 |
| ACE2 | HSF1 | 0.432163732 |
| SWI4 | SWI5 | 0.200020088 |
| SWI4 | SWI6 | 0.35768221 |
| SWI4 | MBP1 | 0.213346764 |
| SWI4 | STB1 | 0.215075917 |
| SWI4 | FKH1 | 0.277864065 |
| SWI4 | FKH2 | 0.326079244 |
| SWI4 | NDD1 | 0.16672633 |
| SWI4 | MCM1 | 0.228995585 |
| SWI4 | ABF1 | 0.16068576 |
| SWI4 | CBF1 | 0.19898189 |
| SWI4 | RAP1 | 0.323818833 |
| SWI4 | REB1 | 0.270482368 |
| SWI4 | STE12 | 0.320334302 |
| SWI5 | FKH2 | 0.329520096 |
| SWI5 | MCM1 | 0.244860201 |
| SWI5 | REB1 | 0.307756859 |
| SWI5 | STE12 | 0.348633234 |
| SWI6 | MBP1 | 0.30583955 |
| SWI6 | STB1 | 0.32667736 |
| SWI6 | FKH1 | 0.442012906 |
| SWI6 | FKH2 | 0.483047343 |
| SWI6 | NDD1 | 0.287393258 |
| SWI6 | MCM1 | 0.374051579 |
| SWI6 | ABF1 | 0.304132418 |
| SWI6 | REB1 | 0.428232107 |
| SWI6 | STE12 | 0.480789074 |
| MBP1 | STB1 | 0.168895212 |
| MBP1 | FKH1 | 0.233766035 |
| MBP1 | FKH2 | 0.283392737 |
| MBP1 | NDD1 | 0.121526234 |
| MBP1 | MCM1 | 0.172403218 |
| MBP1 | ABF1 | 0.126488345 |
| MBP1 | MET31 | 0.273953855 |
| MBP1 | RAP1 | 0.29447829 |
| MBP1 | REB1 | 0.232504717 |
| STB1 | FKH2 | 0.351376072 |
| STB1 | NDD1 | 0.183789962 |
| SKN7 | HSF1 | 0.63765379 |

| | | |
|---|---|---|
| SKN7 | YAP1 | 0.431132581 |
| FKH1 | FKH2 | 0.489508263 |
| FKH1 | NDD1 | 0.261916798 |
| FKH1 | MCM1 | 0.333256997 |
| FKH1 | ABF1 | 0.271478263 |
| FKH1 | RAP1 | 0.481893986 |
| FKH1 | REB1 | 0.39131322 |
| FKH2 | NDD1 | 0.319452542 |
| FKH2 | MCM1 | 0.375321032 |
| FKH2 | ABF1 | 0.283802259 |
| FKH2 | RAP1 | 0.531015871 |
| FKH2 | REB1 | 0.408345439 |
| FKH2 | STE12 | 0.467480448 |
| NDD1 | MCM1 | 0.20998625 |
| NDD1 | ABF1 | 0.13246564 |
| NDD1 | RAP1 | 0.293452199 |
| NDD1 | REB1 | 0.242339652 |
| NDD1 | STE12 | 0.284546001 |
| MCM1 | ABF1 | 0.197601091 |
| MCM1 | MET31 | 0.378656929 |
| MCM1 | REB1 | 0.335792703 |
| MCM1 | STE12 | 0.39270085 |
| ABF1 | BAS1 | 0.229871436 |
| ABF1 | CBF1 | 0.179409718 |
| ABF1 | GCN4 | 0.147673229 |
| ABF1 | GCR2 | 0.194112306 |
| ABF1 | HAP2 | 0.126568578 |
| ABF1 | HAP4 | 0.130782244 |
| ABF1 | MET31 | 0.274035349 |
| ABF1 | RAP1 | 0.293649063 |
| ABF1 | REB1 | 0.245824638 |
| CAD1 | YAP1 | 0.566605197 |
| GCR2 | REB1 | 0.379279221 |
| HAP2 | HAP3 | 0.285251722 |
| HAP2 | HAP4 | 0.241337504 |
| HAP3 | HAP4 | 0.336723095 |
| HSF1 | MSN4 | 0.534651436 |
| LEU3 | MET31 | 0.653046464 |
| LEU3 | RAP1 | 0.605344561 |
| MET31 | RAP1 | 0.609837895 |
| MET31 | REB1 | 0.482888431 |
| RAP1 | REB1 | 0.435230415 |

**Supplementary Table 3. SRF Targets**

| Validated SRF targets | | Possible False Negative |
|---|---|---|
| SRF | | ACVR1B |

| |
|---|
| NKX25 |
| ACTR3 |
| AOC3 |
| RHOE |
| ATP2A2 |
| CFL1 |
| CFL2 |
| CORO1A |
| DSTN |
| DTNA |
| ENAH |
| PDLIM5 |
| HSPB7 |
| ITGA5 |
| ITGB1BP2 |
| PFN1 |
| PLN |
| SDC4 |
| TGFB1I1 |
| TLN1 |
| TNNC1 |
| TRIP6 |
| COPEB |
| ELF5 |
| ETV1 |
| FHL2 |
| HOXB5 |
| LEF1 |
| NFATC4 |
| NFYB |
| TCFAP2B |
| WWTR1 |
| ADM |
| CTGF |
| DUSP6 |
| GPC4 |
| MRGPRF |
| P2RX1 |
| RRAD |
| TM4SF13 |
| BIN1 |
| DNAJB1 |
| MRVI1 |
| CAR3 |
| UROD |
| GALNT3 |
| IMPACT |

| |
|---|
| DVL2 |
| FEN1 |
| NM_008273 |
| SLC2A4 |
| CDH11 |
| HNRPAB |
| NM_010698 |
| EEF1B2 |
| NM_019583 |
| NM_026307 |
| NM_027877 |
| IL13RA1 |
| NDUFS1 |

| |
|---|
| LZF |
| SHKBP1 |

**Supplementary Table 4. C/EBP-β Targets Identified by COGRIM**

| | Gene | Max Fold Change in ChIP-chip data | Max Fold Change in expression data |
|---|---|---|---|
| **Validated Targets Predicted by COGRIM** | Aldh1a1* | 8.5 | 2.5 |
| | Bcap37* | 1.3 | 1.5 |
| | Car3* | 2.1 | 3.9 |
| | Dnm2* | 1.3 | 4.9 |
| | Es1* | 1.5 | 2.1 |
| | Fkbp11* | 1.8 | 1.7 |
| | Gstt1* | 1.3 | 1.6 |
| | Grb2* | 1.8 | 2.6 |
| | Krt1-18* | 1.2 | 10.7 |
| | Pepck1* | 2.8 | 1.4 |
| | Rhob* | 1.6 | 1.5 |
| | Rnf19* | 1.3 | 1.3 |
| | S100a10* | 3.0 | 2.0 |
| | Saa1* | 1.4 | 101.9 |
| | | | |
| **Potential Targets Predicted by COGRIM** | Anxa5* | 6.7 | 1.9 |
| | Tcp1 | 4.3 | 1.2 |
| | Oaz1 | 4.0 | 1.6 |
| | Cxcl12 | 3.8 | 1.5 |
| | Gstm1 | 3.3 | 1.8 |
| | Ier2 | 3.0 | 1.2 |
| | H2-Bf | 2.5 | 1.3 |
| | H3f3b | 2.4 | 1.6 |
| | Pabpc1 | 2.1 | 2.6 |
| | Cdc42 | 2.1 | 1.3 |
| | Arpc1b | 2.1 | 1.6 |
| | Aqp8 | 1.9 | 1.6 |
| | Chd1* | 1.6 | 1.6 |
| | Rnase1 | 1.5 | 3.5 |
| | Acsl1 | 1.5 | 3.9 |
| | Ppp2cb | 1.4 | 2.3 |
| | Ptk2 | 1.3 | 4.2 |
| | Rnase4 | 1.2 | 1.8 |

| | | | |
|---|---|---|---|
| | | | |

*genes also selected in Friedman et al. (2004)

**Table 5. C/EBP-β Targets Identified by COGRIM based on expression data alone**
*experimentally validated C/EBP-beta targets in Friedman et al. (2004)

| Gene | Max Fold Change in Chip-chip data | Max Fold Change in expression data |
|---|---|---|
| Dnm2 * | 1.30 | 4.90 |
| Es1 * | 1.50 | 2.10 |
| Pepck1 * | 2.80 | 1.40 |
| Krt1-18 * | 1.20 | 10.70 |
| Saa1* | 1.40 | 101.90 |
| | | |
| Ier2 | 3.00 | 1.20 |
| Pabpc1 | 2.10 | 2.60 |
| Ptk2 | 1.30 | 4.20 |
| Oaz1 | 4.00 | 1.60 |
| Prss2 | 1.11 | 2.34 |
| Rcor1 | 1.25 | 2.06 |
| Ifrd1 | 1.05 | 3.23 |
| Zbtb17 | 1.12 | 11.99 |
| Acadm | 1.11 | 11.98 |
| Rnf130 | 1.15 | 1.33 |
| Tgif | 1.17 | 2.65 |
| Cel | 1.26 | 1.11 |
| Ctrl | 1.32 | 2.56 |
| Nme2 | 1.13 | 2.43 |
| Cmkor1 | 1.27 | 4.60 |
| Sort1 | 1.38 | 5.11 |
| Coro1c | 1.18 | 1.14 |
| Dnajb6 | 1.25 | 5.12 |
| Ets2 | 1.14 | 1.78 |
| Tceal8 | 1.68 | 1.83 |
| H2afz | 1.26 | 2.48 |

**Table 6. Identify Activators and Repressors**
Statistical significance of the activator was determined by significant positive beta with 95% positive posterior interval, and similarly, repressor was determined by significant negative beta with 95% negative posterior interval. Sixteen TFs were identified as activators and one repressor. Also, we use another method to determine the activation or repression, and check the consistency. In the second method, statistical significance of the activator was determined by computing correlation coefficients between all TFs and all gene clusters, and taking 5% positive tail of the distribution of correlation coefficients; similarly, repressor was determined by taking 5% negative

tail. The consistent beta and expression correlation suggests that the beta parameter in our model can be used as an indicator of TFs' activity.

| TF name | β | Expression Correlation between TF and its regulons | | Descriptions from SGD & Literature |
|---|---|---|---|---|
| | | B+/C+ | B-/C+ | |
| SWI5 | 0.35 | 0.36 | 0.53 | activates transcription of cell cycle genes. |
| SWI6 | 0.63 | 0.63 | 0.67 | activates transcription of cell cycle genes. |
| FKH1 | 0.57 | 0.77 | 0.75 | activates transcription of cell cycle genes. |
| FKH2* | 0.64 | 0.51 | 0.57 | activates transcription of cell cycle genes. |
| BAS1* | 0.59 | 0.61 | 0.67 | Myb-related transcription factor involved in regulating basal and induced expression of genes of the purine and histidine biosynthesis pathways |
| CAD1 | 0.87 | 0.69 | 0.74 | AP-1-like bZIP transcriptional activator involved in multiple stress responses, iron metabolism, and pleiotropic drug resistance; controls a set of genes involved in stabilizing proteins |
| HAP3* | 0.46 | 0.41 | 0.56 | a transcriptional activator and global regulator of respiratory gene expression |
| HAP4 | 0.41 | 0.84 | 0.80 | a transcriptional activator and global regulator of respiratory gene expression |
| HSF1 | 0.89 | 0.55 | 0.59 | activates multiple genes in response to heat shock |
| LEU3* | 0.81 | 0.60 | 0.64 | involved in branched chain amino acid biosynthesis and ammonia assimilation |
| MET31* | 0.72 | 0.55 | 0.56 | involved in regulating expression of the methionine biosynthetic genes |
| MSN4 | 0.56 | 0.59 | 0.64 | Transcriptional activator related to Msn2p; activated in stress conditions, which results in translocation from the cytoplasm to the nucleus; binds DNA at stress response elements of responsive genes, inducing gene expression |
| RAP1* | 0.75 | 0.55 | 0.58 | DNA-binding protein involved in either activation or repression of transcription |

| | | | | |
|---|---|---|---|---|
| REB1* | 0.58 | 0.56 | 0.57 | RNA polymerase I enhancer binding protein |
| STE12 | 0.69 | 0.83 | 0.84 | activates genes involved in mating or pseudohyphal/invasive growth pathways |
| YAP1 | 0.50 | 0.58 | 0.54 | bZip transcription factor required for oxidative stress tolerance |
| RME1* | -0.45 | -0.51 | -0.46 | Zinc finger protein involved in control of meiosis; prevents meiosis by repressing IME1 expression |

* COGRIM identified seven more activators as well as one repressor RME1 when comparing to GRAM [4].

**Supplementary Materials**

Supplementary Figure 1.
Based on our estimated regulation indicators $C_{ij}$, we construct the functional regulatory network with 2298 TF-gene interactions between 39 TFs and 1542 functional target genes. The edges represent the regulatory activity of TF to target genes, the box nodes (red) represent transcription factors labeled with TF names, other nodes represent the target genes and the gene names are not shown. The regulatory network is illustrated with LGL [38].